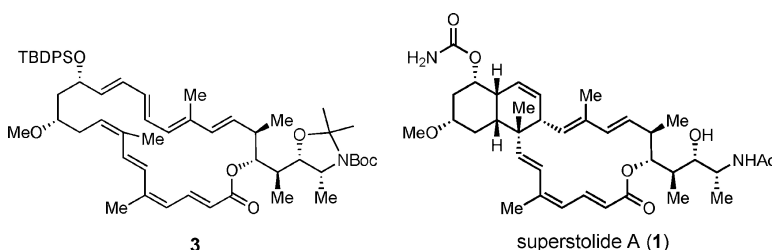


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## Total Synthesis of (+)-Superstolide A

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Superstolides A (**1**) and B (**2**) are structurally novel macrolides isolated from the New Caledonian sponge *Neosiphonia superstes* (Figure 1).<sup>1</sup> The superstolides are highly cytotoxic toward several cancer cell lines including murine P388 leukemia cells (IC<sub>50</sub> = 3 ng/mL for **1** and **2**), human nasopharyngeal cells (IC<sub>50</sub> = 5 ng/mL for **2**), and non-small-cell lung carcinoma cells (IC<sub>50</sub> = 4 ng/mL for **1** and **2**). Consequently, they have attracted attention as targets for synthesis and further biological evaluation.<sup>2,3</sup> We report herein a highly stereoselective total synthesis of (+)-superstolide A (**1**) by a route that is likely biomimetic in nature,<sup>4,5</sup> and which proceeds via the transannular Diels–Alder reaction of the 24-membered octaene **3**.<sup>6</sup>

We intended from the outset that the cis-fused bicyclic octahydronaphthalene unit of **1** would be established by a Diels–Alder reaction performed either in the intramolecular<sup>2a</sup> or transannular manifolds.<sup>2b</sup> Among the attractive features of a plan to pursue a transannular Diels–Alder reaction of the 24-membered octaene **3** is that certain TDA reactions are known to be much more stereoselective than analogous IMDA reactions.<sup>6–8</sup> However, counter balancing this potential advantage is the chemical sensitivity of the two conjugated tetraene units of **3**. Therefore, the synthesis was designed to proceed from the four building blocks **4–7** such that the timing of the Diels–Alder reaction relative to the macrocyclization event (cf., use of **3** vs **8** as key intermediates) could be adjusted late in the synthesis. In practice, the synthesis that proceeds by way of macrocyclic octaene **3** has proven successful and is described herein.

The synthesis of phosphonium salt **4** commenced with the asymmetric allylation (96:4 d.r.) of aldehyde **9**<sup>9</sup> (Scheme 1). O-Methylation of the resulting secondary alcohol followed by ketal hydrolysis then provided diol **10**. After differential protection of the two hydroxyl groups of **10**, the derived triether **11** was subjected to ozonolysis and Horner–Wadsworth–Emmons olefination according to the Still–Gennari procedure<sup>10</sup> to give the (*Z*)-enoate **12** in 76% yield over four steps. Deprotection of the trityl ether and oxidation of the resulting hydroxyl group with SO<sub>3</sub>–pyridine–DMSO<sup>11</sup> provided aldehyde **13** (90%), which was then elaborated to **14** (79% yield) via Takai olefination (CHI<sub>3</sub>, CrCl<sub>2</sub>)<sup>12</sup> and DIBAL–H reduction. Finally, conversion of **14** to the corresponding allylic bromide **15** (98%), and then treatment of **15** with Bu<sub>3</sub>P in CH<sub>3</sub>CN, provided phosphonium salt **4** (89%).

Horner–Wadsworth–Emmons olefination of hydroxybutenolide **16**<sup>13</sup> with the β-phosphonoester **17**<sup>14</sup> provided **18** in 76% yield (Scheme 2). Reduction of the carboxylic acid via the mixed anhydride and then oxidation of the primary alcohol by using the Dess–Martin procedure<sup>15</sup> provided **6** in 85% yield. This aldehyde (1.2 equiv) was then coupled with phosphonium salt **4** (NaHDMS, THF, –78 °C, 87% yield) and the β-trimethylsilylethyl ester was deprotected by treatment with TASF in DMF (75% yield)<sup>16</sup> to give the isomerically pure C(1)–C(15) pentaene fragment **20**.

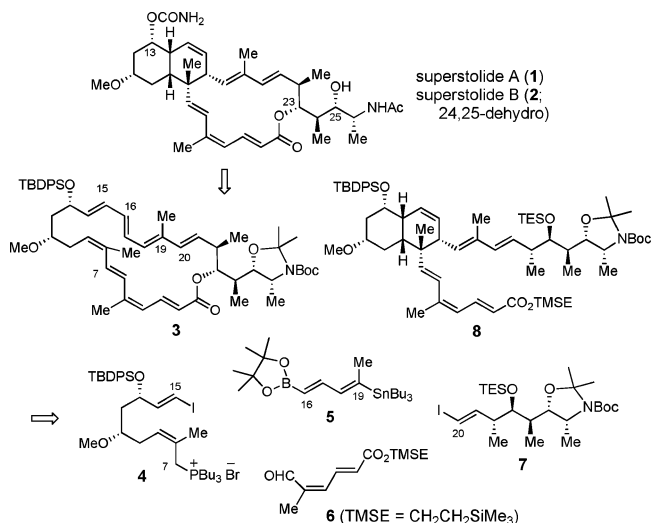
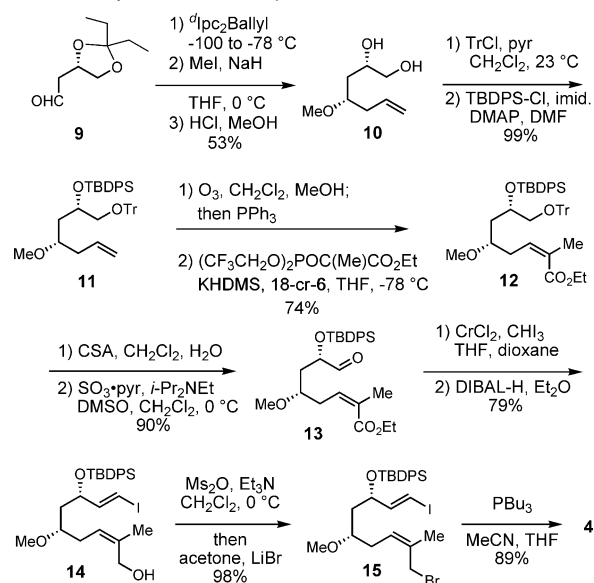


Figure 1. Superstolides A and B; retrosynthetic analysis.

### Scheme 1. Synthesis of Phosphonium Salt **4**

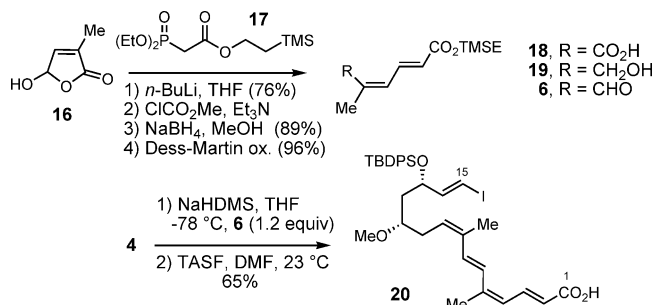
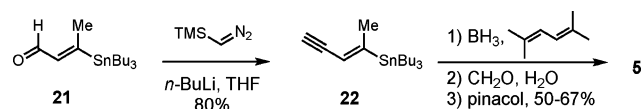
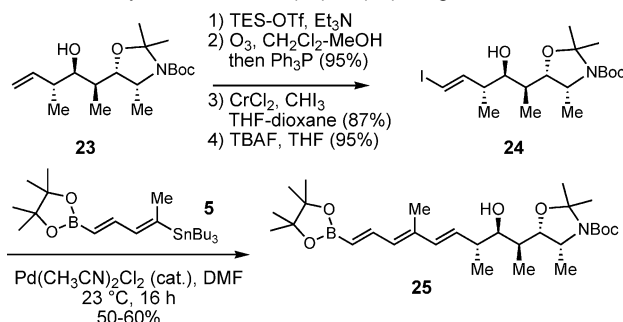
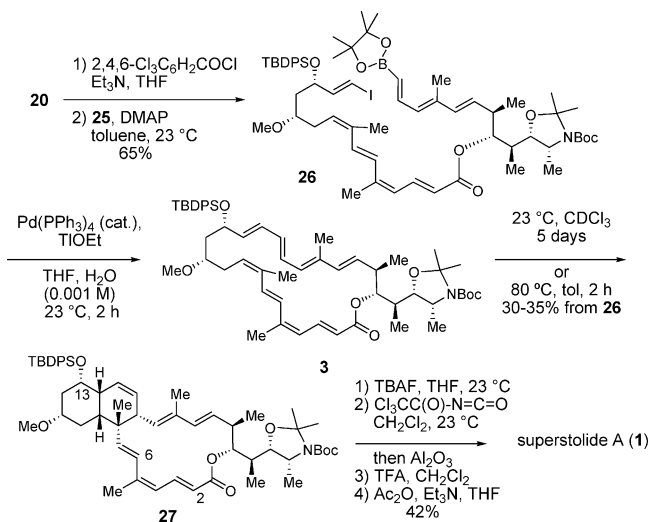


The bimetallic diene linchpin **5** was synthesized starting from vinylstannane **21**<sup>17</sup> as outlined in Scheme 3.<sup>18,19</sup> Alkynylation of **21** by treatment with lithiotrimethylsilyldiazomethane<sup>20</sup> followed by hydroboration of **22** according to Snieckus' procedure<sup>21</sup> provided **5** in good yield (50–67% from **22**). All other methods studied for conversion of **22** to **5** were unsuccessful.<sup>22</sup>

The C(16)–C(29) fragment **25** was synthesized starting from alcohol **23**<sup>2c</sup> (Scheme 4). Temporary protection of C(25)–OH as a TES ether followed by ozonolysis of the alkene, treatment of the resulting aldehyde with CrCl<sub>2</sub>–CHI<sub>3</sub>,<sup>23</sup> and deprotection of C(25)–OH provided **24** in 79% yield. Treatment of a mixture of **24** and

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**Scheme 2.** Synthesis of Aldehyde **6** and Wittig Coupling with **4****Scheme 3.** Synthesis of Bimetallic Diene Linchpin **5****Scheme 4.** Synthesis of the C(16)–C(29) Fragment **25****Scheme 5.** Completion of the Total Synthesis of Superstolide A

linchpin **5** with catalytic PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in DMF then provided vinylboronic ester **25** in 50–60% overall yield.<sup>24</sup>

Coupling of carboxylic acid **20** and alcohol **25** using the Yamaguchi esterification procedure<sup>25,26</sup> (**20**, trichlorobenzoyl chloride, Et<sub>3</sub>N, then **25** and DMAP) provided ester **26** in 65% yield (Scheme 5). Treatment of a 0.001 M solution of **26** in wet THF with TIOEt and catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> effected an intramolecular Suzuki reaction<sup>27,28</sup> that provided the macrocyclic octaene **3** (35–40% yield), plus products believed to arise from bimolecular cross coupling of **26**. Macrocyclic **3** underwent highly diastereoselective transannular Diels–Alder cyclization at ambient temperature over 5 days, or in 2 h at 80 °C, to give **27** as the only observed cycloadduct in 30–35% overall yield from **26**. Interestingly, <sup>1</sup>H NMR analysis of **27** at 23 °C revealed a dynamic mixture of Boc rotamers along with conformational isomers within the newly

formed 16-membered ring, as evidenced by doubling of the <sup>1</sup>H resonance for many protons including H(3) and H(6) and confirmed by variable temperature NMR studies. Finally, sequential treatment of **27** with TBAF (to remove the TBDPS ether), trichloroacetyl isocyanate,<sup>29</sup> TFA in CH<sub>2</sub>Cl<sub>2</sub> (to remove the Boc and acetonide protecting groups) and then Ac<sub>2</sub>O and Et<sub>3</sub>N provided synthetic (+)-superstolide A (**1**) in 42% yield from **3**. The spectroscopic properties of synthetic **1** were in complete agreement with data previously published for the natural product.<sup>1</sup>

In summary, a convergent and highly stereocontrolled synthesis of superstolide A has been accomplished via the highly diastereoselective transannular Diels–Alder cyclization of macrocyclic octaene **3** which constitutes another example of a transannular Diels–Alder reaction that displays much higher diastereoselectivity than corresponding IMDA counterparts.<sup>2a,7,8</sup>

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

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