

# Synthesis of the Entire Framework of Tartrolon B Utilizing a Silicon-Tethered Ring-Closing Metathesis Strategy

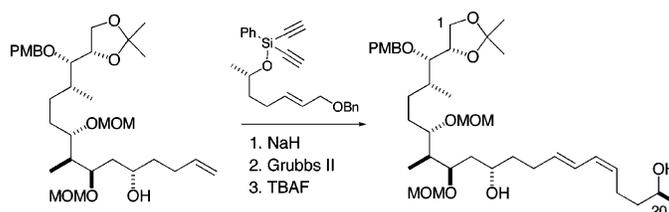
Yi Jin Kim and Daesung Lee\*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue,  
Madison, Wisconsin 53706

dlee@chem.wisc.edu

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## ABSTRACT



A tandem ring-closing metathesis (RCM) of silaketal-tethered dienynes gives rise to bicyclic siloxanes, which upon removal of the silicon tether afford dienediol skeletons with a stereodefined *E,Z*-1,3-diene motif. The implementation of this methodology has led to the construction of the entire C1–C21 linear carbon skeleton of tartrolon B.

Tartrolon B (**1**), a boron-containing  $C_2$ -symmetrical macrolide, is an ion-carrier antibiotic first isolated in 1994 by Höfle and co-workers from the myxobacterium *Sorangium cellulosum* strain So ce678.<sup>1</sup> Notably, the fermentation of this strain may be directed to afford both **1** and tartrolons A1–A3 (**2a–c**) (Figure 1), depending on the material of the fermentation vessel (glassware affords **1**, and steel affords its boron-free counterparts **2a–c** as diastereomeric mixtures). Both are, however, inhibitors of Gram-positive bacteria with MIC values of 1  $\mu\text{g/mL}$ , which indicates that the presence of boron is not required for its antibiotic activity.<sup>2</sup> In addition to its promising antibiotic properties, noteworthy structural features of **1** include the C1–C7 fragment, which is also found in structurally related boron-core antibiotics such as boromycin,<sup>3</sup> aplasmomycin,<sup>4</sup> and borophycin.<sup>5</sup> Another prominent structural feature that is of particular interest to our group is the *E/Z*-diene moiety at C14–C17.

This particular 1,3-diene motif, commonly found in natural products, is often constructed via metal-mediated Sonogashira-type alkyne–vinyl halide couplings<sup>6</sup> followed by *Z*-

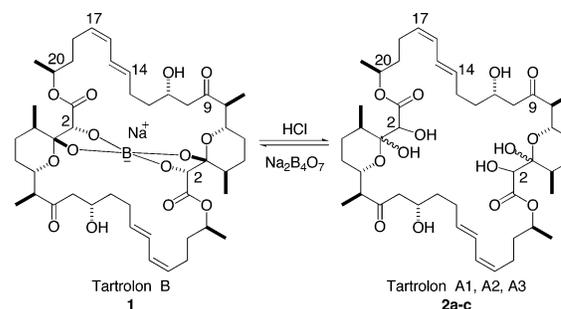


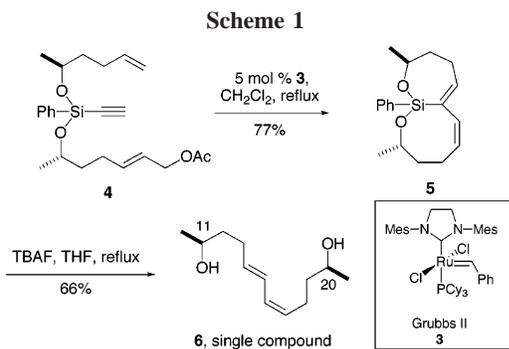
Figure 1. Tartrolons A and B

stereoselective reduction<sup>7,8</sup> of the 1,3-*E*-ene-yne. In the case of Mulzer's total synthesis of tartrolon B, this fragment was constructed through an alkynyllithium addition to acrolein, followed by a Johnson–Claisen rearrangement, and the resulting 1,3-*E*-ene-yne was subjected to the *Z*-selective Boland reduction to furnish the desired *E/Z*-1,3-diene piece.<sup>8</sup> To construct this motif more efficiently, we sought to develop an alternative method, which incorporates a tandem enyne ring-closing metathesis (RCM).<sup>9</sup> Relying on the unique capacity of enyne metathesis to form 1,3-dienes and a novel

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stereochemical control in tandem RCM of dienyne,<sup>10</sup> we envisioned that a silaketal such as **4** would undergo group-selective RCM to furnish bicyclic siloxane **5**, which upon simple protodesilylation can furnish **6** (Scheme 1). Gratify-



ingly, the treatment of **4** with a catalytic amount of catalyst **3**,<sup>11</sup> followed by desilylation, provided a single isomeric dienediol product **6**, a structural equivalent to the C11–C20 fragment of tartrolon B, in good yield. Herein, we report a unique approach for the synthesis of the entire carbon framework of tartrolon B based on the enyne RCM strategy.

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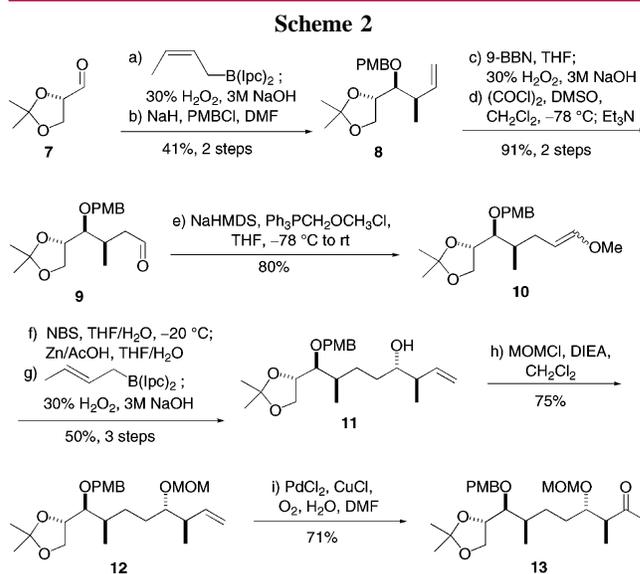
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Because the two-step transformation shown in Scheme 1 could be broadly applicable to the synthesis of related structural motifs, we developed a strategy to synthesize the C1–C21 linear chain of tartrolon B. The preparation of ketone **13** began with asymmetric crotylation<sup>12</sup> of aldehyde **7** to yield the *syn*-crotyl adduct, directly followed by PMB-ether formation to afford **8** (41% over two steps, Scheme 2). This intermediate was then subjected to hydroboration



followed by Swern oxidation to give aldehyde **9** in excellent yields. Homologation of the aldehyde under typical conditions gave rise to the methyl enol ether **10** as a mixture of *E/Z*-isomers (1.5:1 *E/Z*, 80%). After trying several different conditions to convert **10** to the corresponding aldehyde, we chose a two-step protocol using NBS followed by Zn/AcOH, which turned out to be the best conditions to give the desired aldehyde (87%). This aldehyde was then subjected to another asymmetric crotylation<sup>12</sup> to generate *anti*-crotyl adduct **11** in 57% yield. The resulting alcohol was then protected as its MOM-ether (75%) and subjected to Wacker oxidation<sup>13</sup> to give the desired methyl ketone **13** in 71% yield.

The synthesis of **13** set the aldol addition to 4-pentenal to establish the C11 stereocenter and the terminal alkene moiety for the projected tandem dienyne RCM. On the basis of known examples of substrate-controlled aldol reaction using  $\alpha$ -methyl- or  $\beta$ -alkoxy-substituted methyl ketones,<sup>14</sup> we

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**Table 1.** Selectivity in Methyl Ketone Aldol Reactions

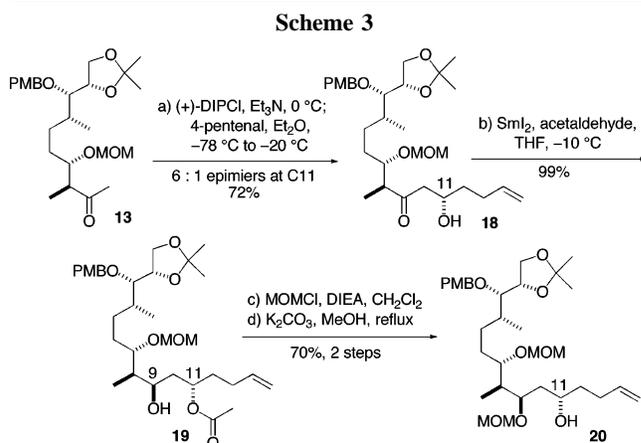
entry	ketone	conditions	product	<i>anti/syn</i> (yield)
1		(-)-DIPCl, Et <sub>3</sub> N 0 °C to -78 °C to -10 °C		1 : 1 (83%)
2		(-)-DIPCl, Et <sub>3</sub> N 0 °C to -78 °C to -10 °C		1.5 : 1 (58%)
3		(-)-DIPCl, Et <sub>3</sub> N 0 °C to -78 °C to -10 °C		1 : 1 (67%)
4		(-)-DIPCl, Et <sub>3</sub> N 0 °C to -78 °C to -20 °C		2.2 : 1 (61%)
5		(+)-DIPCl, Et <sub>3</sub> N 0 °C to -78 °C to -20 °C		6 : 1 (72%)

pursued an enol borinate addition to 4-pentenal using (–)-chlorodiisopinocampheylborane (Table 1). Notably, in Mulzer's evaluation of this chiral boron-mediated aldol chemistry on related systems,<sup>8a</sup> the asymmetric induction was substrate-controlled rather than reagent-controlled (the chiral Ipc's on boron did not influence the absolute sense of chirality of the product).  $\beta$ -Alkoxy-substituted methyl ketones have been shown to yield 1,5-*anti* aldol adducts in many reported cases, although in varying degrees with respect to the overall sense of asymmetric induction depending on the nature of the substrate and the conditions used.<sup>8a,14,15</sup> Because the chirality of the reagent was not crucial to the asymmetric induction, we arbitrarily chose (–)-DIPCl to generate the enol borinate from various ketones (Table 1, entries 1–3). Unfortunately, the stereochemical outcome turned out to be less predictable in these cases, providing aldol products **16**–**18** all in nearly a 1:1 mixture of the two epimers at C11. On the basis of literature precedence, substrates containing the tetrahydropyran moiety (**14**)<sup>8a,14f</sup> or the TBS-ether (**15**)<sup>15</sup> as the  $\beta$ -alkoxy substituent should have favored formation of the 1,5-*anti* aldol adduct.

At this point, we set out to investigate further the conditions that might improve the selectivity of the aldol reaction. We thus lowered the reaction temperature from –10 °C to –20 °C and changed the (–)-DIPCl to (+)-DIPCl (Table 1, entries 4 and 5). To our pleasant surprise, both factors turned out to be important, giving much higher (6:1) selectivity for the aldol product **18**. These findings indicate that although switching the chirality of the diisopinocampheylborane does not change the absolute sense of the asymmetric induction, the degree in which it allows the favored diastereomer to be formed over the other is consider-

able. Furthermore, a change in reaction temperature from –10 °C to –20 °C significantly affects the stereoselectivity, as noted in the final product distribution.

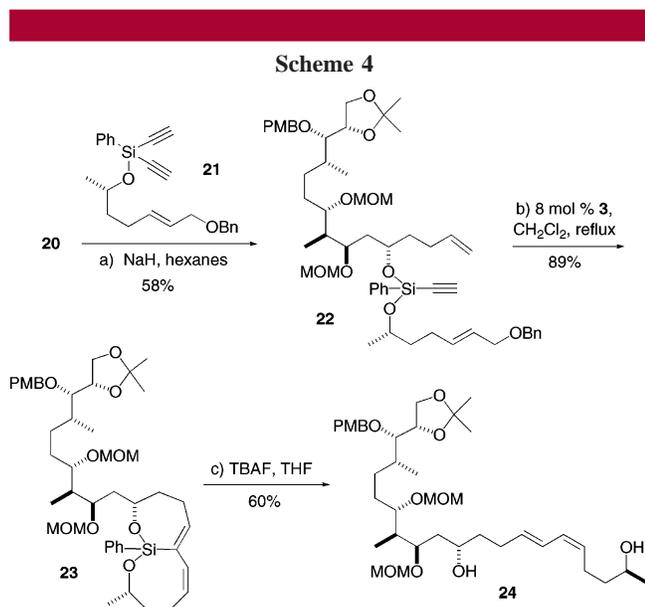
Upon establishing improved conditions for the aldol reaction, we continued to pursue the proposed route to investigate the key RCM step. Initially, we envisioned that aldol product **18** could be directly used for the silaketal formation utilizing conditions developed in our laboratory (1 equiv of silyl ether **21**,<sup>16</sup> with 10 mol % of NaH in hexanes).<sup>17</sup> To our disappointment however, under such basic conditions the transient silaketal underwent rapid elimination to afford the  $\alpha,\beta$ -unsaturated ketone. Thus, we had to revise our plan to mask the ketone functionality in  $\beta$ -hydroxy ketone **18** prior to silaketal formation to avoid the elimination problem.  $\beta$ -Hydroxy ketone **18** was therefore subjected to Evans–Tishchenko<sup>18</sup> conditions to afford the  $\beta$ -acetoxy alcohol **19** in 99% yield (Scheme 3). The C9 hydroxyl group



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was then protected as its MOM-ether, and the acetoxy group was removed to reveal the required C11-hydroxyl group in **20** (84% for each step).

As expected, alcohol **20** reacted smoothly with silyl ether **21** to give desired silaketal **22** in 58% yield as a mixture of two diastereomers, which is the consequence of creating an additional stereogenic center at the silicon (Scheme 4).



Silaketal **22** was designed such that the ring closure can occur in a group-selective fashion;<sup>19</sup> catalyst initiation should occur

(16) For the preparation of silyl ether **21**, see Supporting Information.

at the most accessible terminal alkene, where the first enyne ring closure should generate a seven-membered ring followed by an eight-membered ring closure to furnish bicycle **23**. When **22** was subjected to typical RCM conditions with catalyst **3** (8 mol %), the desired bicyclic siloxane **23** was obtained in 89% yield. Removal of the silicon tether was achieved simply upon treatment with TBAF, affording **24** (60%), which contains the entire C1–C21 carbon framework of the monomeric seco-acid of tartrolon B.

In summary, we have demonstrated that a temporary silicon-tethered tandem RCM can be utilized effectively to construct the C11–C21 *E/Z*-1,3-diene-containing fragment of tartrolon B. This fully functionalized C1–C21 diol, **24**, is envisioned to undergo a few protecting group and oxidation state maneuvers to generate the monomeric seco-acid appropriate for a final dimerization and introduction of the boron core to deliver the total synthesis of tartrolon B. Efforts toward these final stages of a total synthesis of tartrolons are currently under progress, and a full account of the total synthesis will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization information of representative compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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