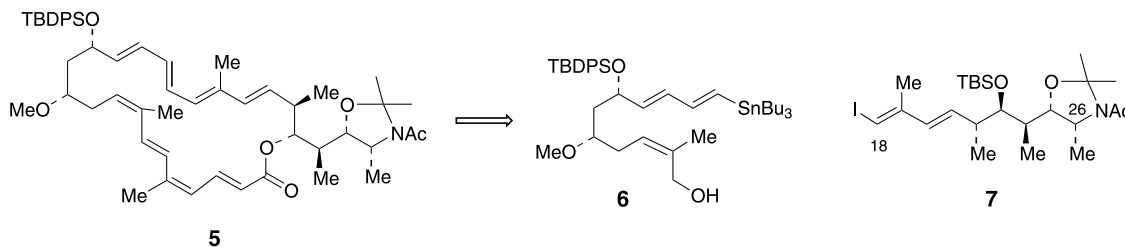


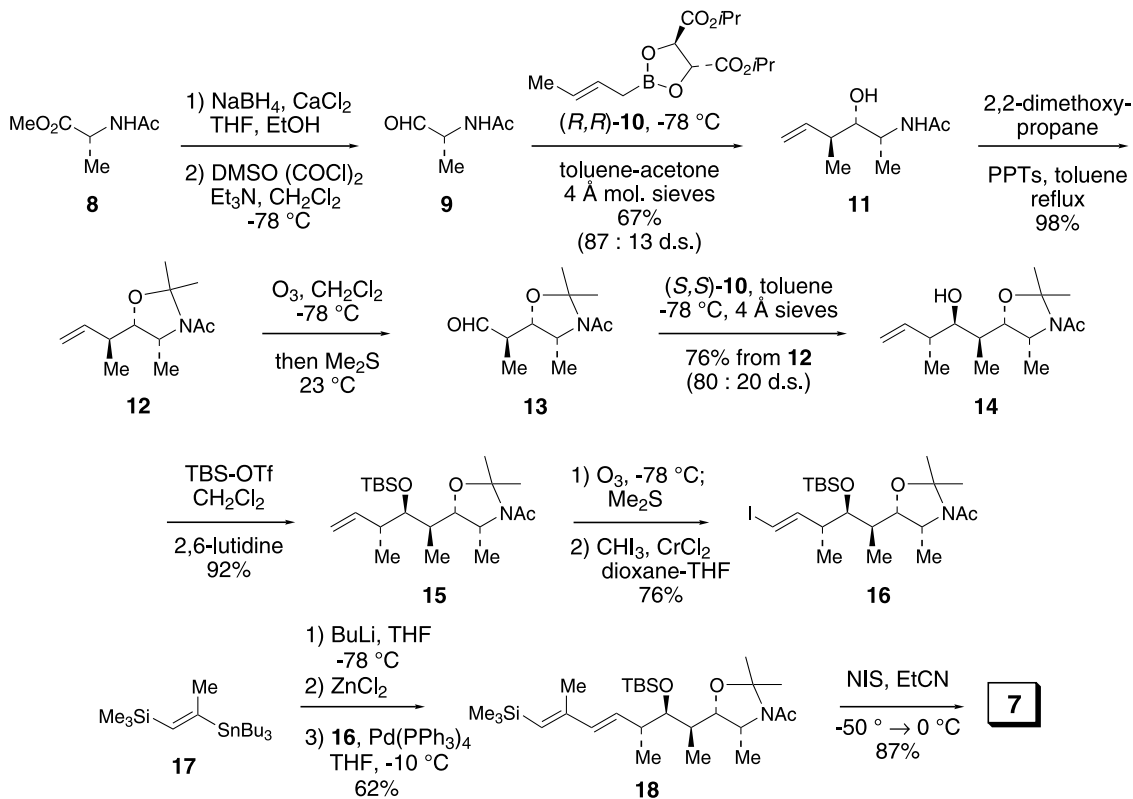


Our current strategy for the synthesis of **1** calls for the key IMDA reaction to be performed at a late stage of the synthesis, ideally at the stage of macrocycle **5** after the major fragments are coupled. This approach would constitute an interesting application of the transannular Diels–Alder reaction<sup>10</sup> in the ring contraction mode,<sup>11</sup> thereby facilitating construction of the highly unsaturated 16-membered ring of the natural product target and minimizing functional group incompatibility problems during the fragment assembly sequence.<sup>12</sup> We envisage that macrocycle **5** will be accessible from precursors **6** and **7**. Towards this goal, we report herein our first generation synthesis of the C(18)–C(26) dienyl iodide fragment **7**.



The synthesis of **7** originates from *N*-acetyl D-alanine methyl ester,<sup>13</sup> which was reduced to the *N*-acetyl alaninol in 88% yield by using NaBH<sub>4</sub> and CaCl<sub>2</sub> in a 1:2 THF/ethanol co-solvent mixture.<sup>14</sup> Oxidation of the alcohol using the standard Swern protocol<sup>15</sup> then provided *N*-acetyl-D-alanine **9**. In order to avoid potential problems with racemization of the *N*-acetylamino aldehyde, intermediate **9** was used directly without purification in the subsequent diastereoselective (*E*)-crotylboration reaction using (*R,R*)-**10**.<sup>16,17</sup> Owing to the poor solubility properties of **9**, it was necessary to perform this reaction in a 8:1 toluene/acetone co-solvent mix-

ture. Accordingly, the desired diastereomer **11** was obtained in up to 67% yield and 87:13 d.s. from the alaninol intermediate. Fortunately, the two diastereomers could be separated by recrystallization of the mixture from ether/pentane, thereby providing pure **11** for use in the next transformations. Protection of **11** as the acetonide derivative **12** proceeded without complication. After ozonolytic cleavage of the vinyl group of **12**, the stage was set for a second crotylboration reaction, this time employing the (*S,S*)-enantiomer of the crotylboronate reagent **10**. The targeted 3,4-*anti*-4,5-*syn* diastereomer **14** was obtained, as expected,<sup>16</sup> as the major product. However, we were surprised to find that the diastereoselectivity of this reaction was only



ference between the aldehyde utilized here (**13**) compared to those in our previous synthetic efforts is that the  $\beta$ -alkoxy group is constrained with a cyclic protecting group, which enables the non-bonded lone pairs of electrons on the C(25)-oxygen atom to point towards the tartrate ester in the reaction transition state, a feature that we previously invoked as a reason for diminished diastereoselectivity in the allylboration reaction of  $\alpha$ - and  $\beta$ -alkoxy aldehydes.<sup>20</sup> It is also perhaps worth noting that it is not obvious that Corey's explanation of the origin of asymmetric induction in the allylboration reactions of the tartrate ester modified allylboronates, involving formyl C–H $\cdots$ O hydrogen bonds,<sup>22</sup> is sufficient to rationalize the dependence of reaction diastereoselectivity (or enantioselectivity, for reactions with achiral aldehydes) on the reaction solvent, the presence (and directionality) of  $\beta$ -alkoxy groups, or the conformational rigidity of the tartrate auxiliary.<sup>20,23–25</sup> Thus, we believe that our original dipole-based origin of asymmetric induction continues to merit consideration in the rationalization of the stereochemical course of these reactions.<sup>26</sup>

Protection of the secondary hydroxyl group of **14** as a TBS ether proceeded uneventfully to provide the fully protected intermediate **15** in 92% yield. Ozonolysis of the vinyl group and application of the Takai olefination procedure then provided vinyl iodide **16** in 76% yield.<sup>27</sup> Palladium(0) catalyzed cross coupling of **16** with the vinylzinc species generated by treatment of vinylstannane **17**<sup>28</sup> with BuLi in THF ( $-78^\circ\text{C}$ ) followed by addition of ZnCl<sub>2</sub> then provided the dienyllic silane **18** in 62% yield.<sup>29</sup> Finally, treatment of the dienylsilane unit of **18** with NIS in EtCN at  $-50^\circ\text{C}$  with warming to  $0^\circ\text{C}$  then provided the targeted dienyllic iodide **7** in 87% yield.<sup>30</sup>

In conclusion, a diastereoselective synthesis of dienyllic iodide **7** is described. Further progress towards completion of the total synthesis of superstolide A will be reported in due course.

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