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Synthesis of the C(21)−C(26) Fragment of Superstolide A: Concerning the Stereochemistry of (*E*)-Crotylboration Reactions of Alaninal Derivatives

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A stereoselective synthesis of the C(21)−C(26) fragment of superstolide A has been completed. The absolute and relative stereochemistry of intermediate **14** has been conclusively proven by NMR and X-ray diffraction methods. In the course of this work, it was found that the stereochemistry of **3** had been misassigned in our previously reported synthesis of the C(18)−C(26) segment. This error stems from the unexpected diastereoselectivity in the double asymmetric reaction of *N*-acetyl-D-alaninal **1** and the tartrate ester modified (*E*)-crotylboronate (*R*,*R*)-**2**.

Introduction

We recently reported a synthesis of intermediate **5**, believed to be the C(18)−C(26) fragment of the marine macrolide superstolide A (**6**) (Figure 1).[1] A key reaction in the sequence leading to the presumed **5** was the crotylboration reaction of *N*-acetyl-D-alaninal (**1**) with the diisopropyl (*R*,*R*)-tartrate-modified (*E*)-crotylboronate [(*R*,*R*)-**2**]. This reaction furnished two diastereomeric products in 67% yield, in a ratio of 87:13 favoring what we believed to be the Felkin product **3**. As it became necessary to scale-up the synthesis to advance toward the natural product, the *N*-acetyl protecting group was abandoned because of difficulties encountered in handling **1**, specifically due to the sensitivity of **1** toward racemization and its solubility profile. We decided to switch to the *tert*-butyloxycarbonyl (BOC) protecting group, as this had been employed in the synthesis of the superstolide A C(21)−C(26) fragment published by Zampella and D'Auria.[2] In the course of pursuing the second-generation sequence, it became apparent that the stereochemistry of **3** had been misassigned in our original report, and therefore that the stereochemistry of the C(18)−C(26) fragment **5** was also incorrect. The present paper serves to correct the earlier results. We also provide insights into the stereochemistry of (*E*)-crotylboration reactions of α-amino aldehyde derivatives.

Results and Discussion

The (*E*)-crotylboration of *N*-BOC-D-alaninal (**7**) was performed in toluene at −78 °C with (*R*,*R*)-**2**,[3,4] furnishing homoallylic alcohols **8** and **9** in a 25:75 ratio (Figure 2, entry 2). Surprisingly, the major product of this reaction did not match the major product obtained from the crotylation of **7** performed with Brown's diisopinocampheyl-derived (*E*)-crotylborane[5] (^{d}Ipc)$_2$-**10** (entry 1), which

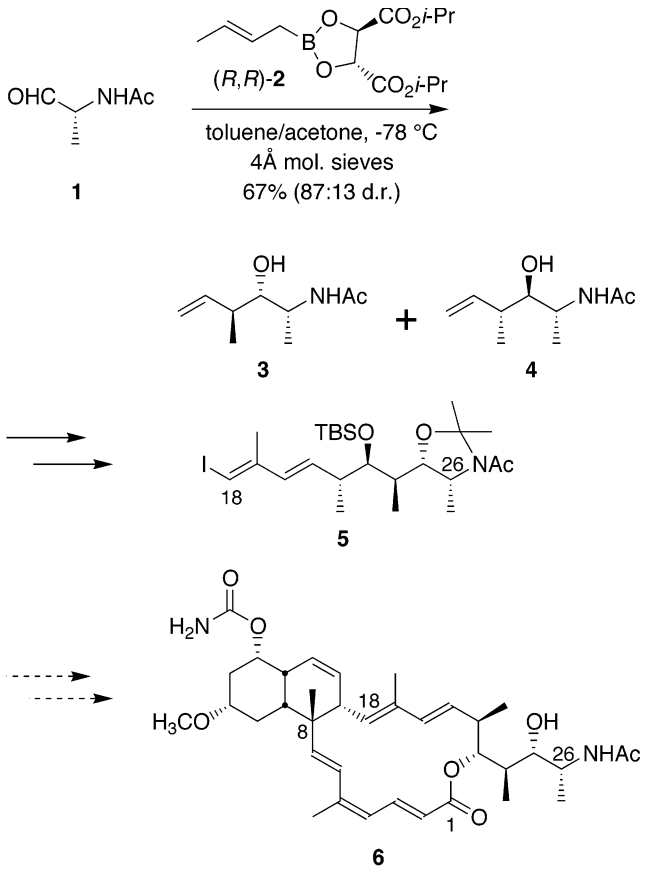

FIGURE 1. Summary of synthesis of presumed superstolide precursor **5**.

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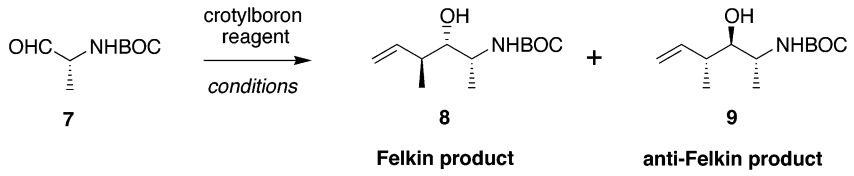


7 **8** **9**

Felkin product **anti-Felkin product**

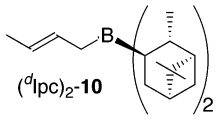
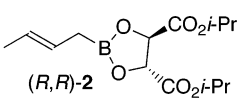
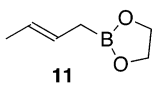
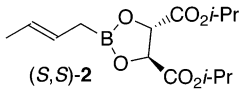
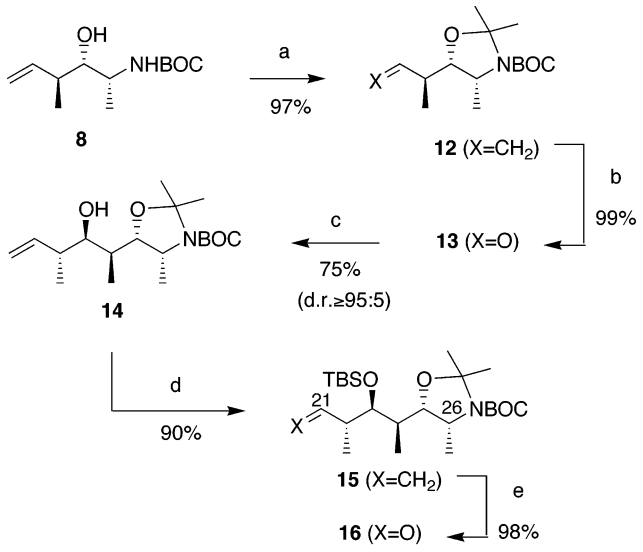
entry	crotylboron reagent	*conditions*	yield	diastereoselectivity **8 : 9**
1	 (^{d}Ipc)$_2$-**10**	BF_3•Et_2O, THF, Et_2O -78 °C, 12 hr; then H_2O_2/NaOH	85%	≥95:5
2	 (*R*,*R*)-**2**	toluene, 4Å mol. sieves, -78 °C, 15 hr; then NaOH	68%	25:75
3	 **11**	toluene, 4Å mol. sieves, -78 °C, 13 hr; then NaOH	53%	25:75
4	 (*S*,*S*)-**2**	toluene, 4Å mol. sieves, -78 °C, 15 hr; then NaOH	68%	≤5:95

FIGURE 2. Crotylation reactions of *N*-BOC-D-alaninal (**7**).

furnished the Felkin product **8** with ≥95:5 selectivity (only one isomer observed).[2,6] To confirm the stereochemistry of the products, alcohol **8** was elaborated to aldehyde **16** (Figure 3), which correlated exactly with the data published for this compound by D'Auria.[2] A single-crystal X-ray structure analysis was performed on product **14** of the second crotylation reaction to unambiguously confirm the relative and absolute stereochemistry of this intermediate. Therefore, the stereochemistry of the C(21)−C(26) fragments **14**, **15**, and **16** are secure. (D'Auria had previously correlated alcohol **14** directly with the natural product.[2])

The question of the divergent diastereoselectivity of the crotylation reactions of *N*-BOC-D-alaninal (**7**) with the tartrate ester modified crotylboronate (*R*,*R*)-**2** and Brown's reagent (^{d}Ipc)$_2$-**10** remained. While the reaction of **7** with (^{d}Ipc)$_2$-**10** provided the Felkin product **8** with excellent selectivity (entry 1), the reaction with (*R*,*R*)-**2** gave the anti-Felkin diastereomer **9** predominantly even though the (*R*,*R*)-tartrate auxiliary should have favored production of **8** in this case (entry 2). This result is a rare exception to the usually observed diastereoselectivity in double asymmetric reactions with the tartrate-modified crotylboronates.[4] This result was all the more surprising since we had studied the allylboration of *N*-BOC serinal acetonide (**36**) and had observed reagent control of stereoselectivity.[7]



Reagents: (a) 2,2-dimethoxypropane, *p*-TsOH (cat.), CH_2Cl_2; (b) O_3, CH_2Cl_2/MeOH, -78 °C, then Me_2S, 23 °C; (c) (*S*,*S*)-**2**, toluene, 4Å M.S., -78 °C; (d) TBS-OTf, *i*-Pr_2NEt, DMF/CH_2Cl_2; (e) O_3, CH_2Cl_2/MeOH, -78 °C, then Me_2S, 23 °C.

FIGURE 3. Synthesis of the superstolide A C(21)−C(26) fragment **15**.

Given the unusual results exhibited by the reaction of (*R*,*R*)-**2** and aldehyde **7**, two more crotylation reagents were examined: the achiral ethylene glycol-protected (*E*)-crotylboronate **11** (Figure 2, entry 3) and the diisopropyl (*S*,*S*)-tartrate-modified (*E*)-crotylboronate (*S*,*S*)-**2** (entry

(5) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
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(7) Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798.

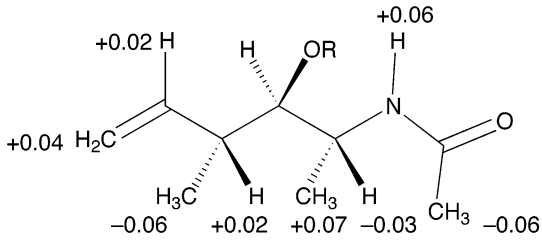


FIGURE 4. Modified Mosher ester analysis of **4** ($\Delta\delta = \delta_{(R)-MTPA} - \delta_{(S)-MTPA}$).

4). The reaction of **7** with (*S*,*S*)-**2** produced the anti-Felkin adduct **9** with excellent selectivity, while the reaction with **11** provided a mixture of diastereomers favoring anti-Felkin **9** in a 75:25 ratio exactly matching that attained by reaction of **7** and (*R*,*R*)-**2**. On the basis of the outcome of these experiments, it was apparent that aldehyde **7** exhibits an extraordinary level of substrate control in the reaction with (*E*)-crotylboronates, with the anti-Felkin product **9** being intrinsically favored. Accordingly, the crotylation with (*S*,*S*)-**2** (entry 4) is deduced to be the matched reaction, while the reaction with (*R*,*R*)-**2** is the mismatched case.[8]

Given the high level of substrate control of *N*-BOC-D-alaninal (**7**) in its reaction with crotylboronates, we reexamined the crotylboration of *N*-acetyl-D-alaninal (**1**). The stereochemistry of the major product of the crotylation reaction of **1** and (*R*,*R*)-**2** was initially assumed to be **3** based on the predictive selectivity trends of the crotylation reactions of *N*,*N*-dibenzyl α-amino aldehydes studied by Hoffman and co-workers,[9] and on the fact that our previous studies of asymmetric allylboration reactions of *N*-BOC serinal acetonide (Garner's aldehyde, **36**) had established stereochemical control by the tartrate ester auxiliary.[7] ^{1}H NMR *J* data obtained for the major product (**4**) of this reaction (and also *J* data obtained for subsequent intermediates) appeared consistent with the originally (mis)assigned structure. However, attempts to verify the stereochemistry of the new hydroxyl group in **4** by application of the modified Mosher (MTPA) ester analysis[10] were inconclusive in assigning the alcohol stereochemistry (Figure 4); similar problems had been encountered in attempts to apply this analysis to the corresponding fragment in the natural product.[11] The stereochemical misassignment in the first generation C(18)−C(26) fragment synthesis was finally conclusively established by deprotection of the Felkin *N*-BOC crotylation product **8** and conversion to the acetamide **3**, which was identified as the minor product of the crotylboration of **1** (Figure 5). A single crystal X-ray structure of the highly crystalline *p*-nitrobenzoyl ester **24** generated from **19** (Figure 6) revealed that all of the stereocenters of the fragment, save the original amino acid center of D-alanine, were inverted relative to the targeted C(21)−C(26) fragment of the natural product. *N*-Acetyl-D-alaninal (**1**) had therefore exhibited similar levels of substrate control as the *N*-BOC analogue (**7**) in the (*E*)-

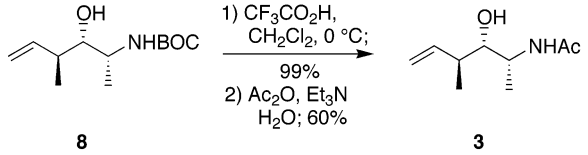
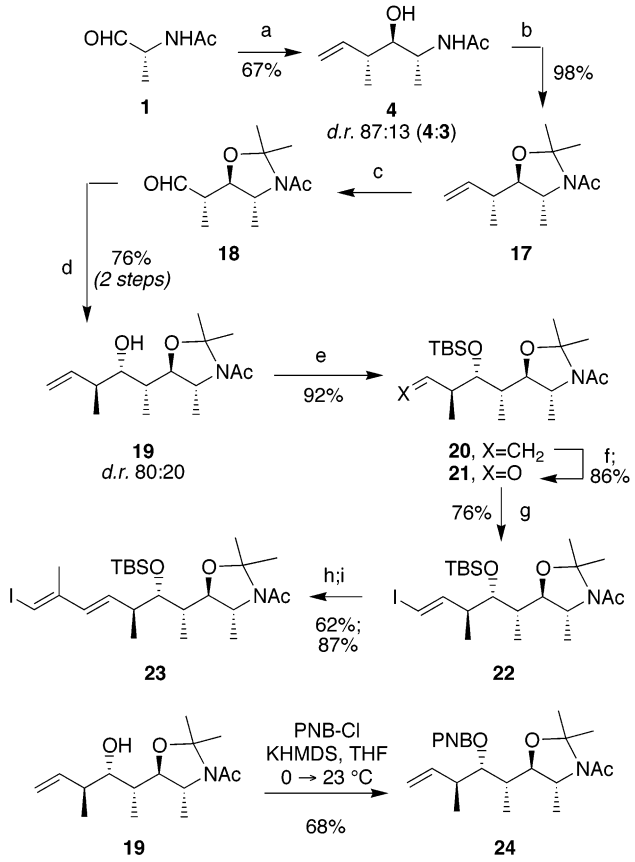


FIGURE 5. Correlation of **8** with **3**.



Reagents: (a) (*R*,*R*)-**2**, 4Å M.S., tol., -78 °C; (b) 2,2-dimethoxypropane, PPTS (cat.), tol., D; (c) O_3, CH_2Cl_2, -78 °C, then Me_2S, 23 °C; (d) (*S*,*S*)-**2**, 4Å M.S., tol., -78 °C; (e) TBS-OTf, 2,6-lutidine, CH_2Cl_2; (f) O_3, CH_2Cl_2, -78 °C, then Ph_3P, 23 °C; (g) $CrCl_2$, CHI_3, THF; (h) Me_3Si(Me)=CH-$SnBu_3$, *n*-BuLi, THF, -78 °C, then $ZnCl_2$, then $Pd(PPh_3)_4$ (cat.), -10 °C; (i) NIS, EtCN, -50 → 0 °C

FIGURE 6. Corrected structures of intermediates in the first generation synthesis of potential superstolide precursors (ref 1) (PNB = *p*-nitrobenzoyl).

crotylation reaction and furnished the undesired anti-Felkin adduct **4** as the major product (Figure 6). Thus, after formation of the *N*,*O*-acetonide **17** and ozonolysis to furnish aldehyde **18**, the second crotylation with the (*S*,*S*)-(*E*)-crotylboronate (*S*,*S*)-**2** was then a challenging mismatched reaction (as would be expected according to other studies of double asymmetric crotylation reactions).[12] Consequently, the Felkin product **19** was obtained with only moderate diastereoselectivity (80:20), with substrate control dominating the enantioselectivity of the reagent. The matched reaction in the *N*-BOC series

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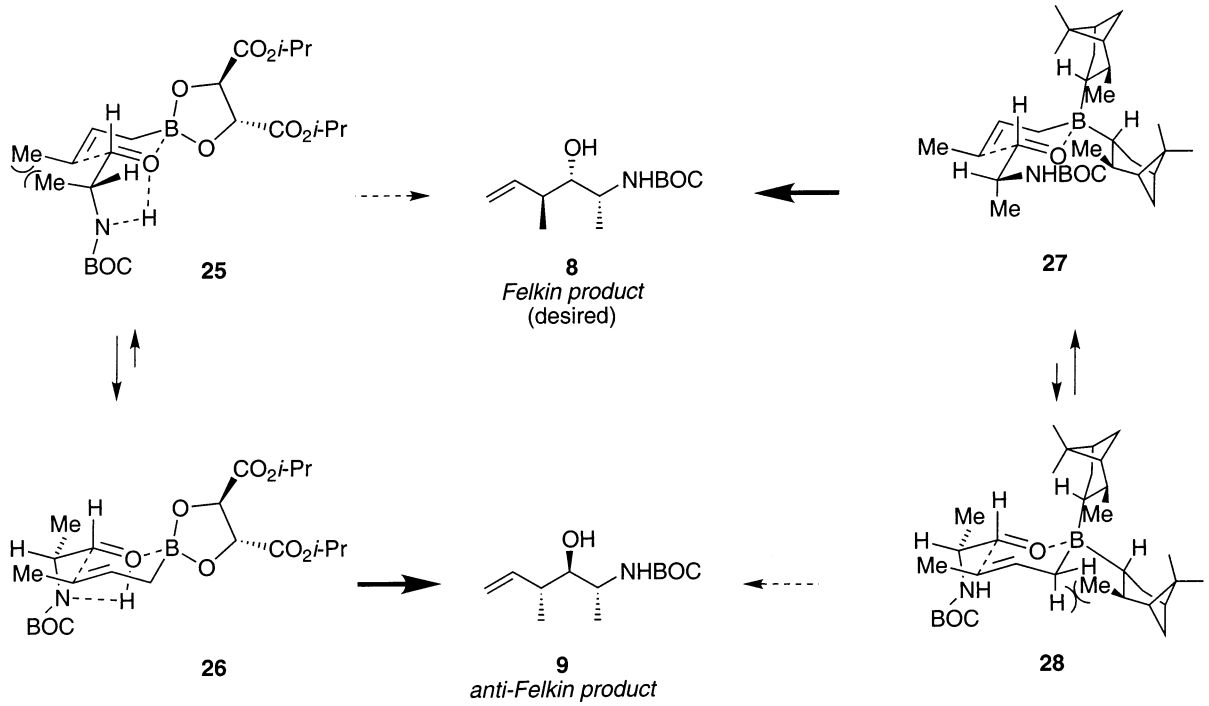

FIGURE 7. Transition state models to explain diastereoselectivity in the reaction of *N*-BOC-D-alaninal (**7**) with modified (*E*)-crotylboron reagents (*R*,*R*)-**2** (**25** vs **26**) and (^{d}Ipc)$_2$-**10** (**27** vs **28**).

(**13** → **14**, Figure 3) gave extremely high levels of Felkin selectivity, as would be predicted by the high selectivity realized in the matched double asymmetric reactions of chiral α-methyl aldehydes and the tartrate ester modified crotylboronates.[12]

We must account for the divergent diastereoselectivity of the diisopinocampheyl−crotylborane and tartrate-modified (*E*)-crotylboronate reactions with the *N*-monoprotected alaninals. In the reaction with the tartrate-modified crotylboronates, aldehyde **7** may assume a transition state rotamer (see **25** and **26**, Figure 7) in which the carbamate group occupies the Felkin-Anh "medium" position, while the methyl plays the role of the "large" substituent.[13] In this case, the flat, sp^2-hybridized carbamate group may adopt a conformation that could be considered sterically smaller than the sp^3-hybridized methyl group. A potential intramolecular hydrogen bond between the carbamate nitrogen atom and aldehyde carbonyl oxygen atom could also act to stabilize this transition state conformation as well (Figure 7). Hydrogen bond and metal-chelate models have been invoked to explain the stereochemistry of nucleophilic additions to *N*-monoprotected α-amino aldehydes.[14−16] In this aldehyde rotamer, addition of (*R*,*R*)-**2** to the normally favored *si* face of aldehyde **7** would result in a deleterious *syn*-pentane type interaction between the two methyl groups, as shown in **25** (Figure 7). This steric strain is relieved in the addition to the *re* face (see transition state **26**), resulting in the predominance of the anti-Felkin product **9**. This analysis also provides a rationalization for the unanticipated anti-Felkin face selectivity of the crotylboration reaction of **7** and the achiral (*E*)-crotylboronate **11** (Figure 2, entry 3). Most surprising, however, is the fact that the (*R*,*R*)-tartrate auxiliary in (*R*,*R*)-**2** did nothing to change the selectivity of the reaction, compared to the result with achiral **11** (Figure 2, entries 2 and 3), despite the electron pair repulsion between the tartrate ester carbonyl and the aldehydic oxygen lone pair in transition state **26**. Such reasoning stems from explanations of the induction of facial selectivity by the diisopropyl tartrate group borne on boron.[17] However, in the case of the reaction of **7** with (^{d}Ipc)$_2$-**10**, the overriding steric bias induced by the highly enantioselective isopinocampheyl ligands in transition states **26** and **27** must be sufficient to override the inherent facial selectivity of the aldehyde to give the predicted Felkin product **8**. One possibility is that the increased Lewis acidity of the boron atom in the Brown reagent may withdraw electron density away from the aldehyde carbonyl, thereby mitigating the energetic significance of the hydrogen bond that we speculate may be involved in **25** or **26**. Thus, a normal Felkin rotamer of the aldehyde could be accessed in **27** and provide the desired product **8** via a highly selective mismatched double asymmetric reaction.

The explanations offered above specifically address the diastereoselectivity of the reactions of (*E*)-crotylboron reagents with monoprotected *N*-acyl α-amino aldehydes. To support our assertions, the crotylboration reaction of *N*,*N*-dibenzyl-D-alaninal **30** was examined for comparison. Reetz had shown that the reaction of **30** with the pinacol-modified (*E*)-crotylboronate was quite Felkin

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(17) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692.

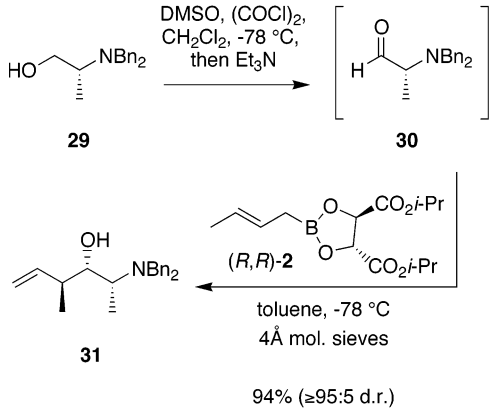

FIGURE 8. Asymmetric (*E*)-crotylboration of **30**.

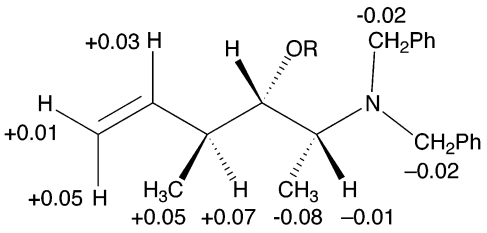

FIGURE 9. Modified Mosher ester analysis of **31** ($\Delta\delta = \delta_{(R)-\text{MTPA}} - \delta_{(S)-\text{MTPA}}$).

selective, furnishing two products in a diastereomeric ratio of 90:10.[18] The reaction of aldehyde **30** with (*R*,*R*)-**2** proceeded as expected for a matched double asymmetric reaction, affording solely the Felkin isomer **31** in high yield (Figure 8). This structure assignment for product **31** is supported by a conclusive modified Mosher (MTPA ester) analysis (Figure 9).

The literature offers limited examples of crotylboration reactions of protected α-amino aldehydes, and other unusual diastereoselectivity phenomena have been observed (Figure 10).[19,20] For instance, the crotylboration of the *N*-BOC-L-prolinal (**32**) with (*Z*)-crotylboron reagents **33a**−**d** favored the Felkin product **34** in all cases (Figure 10, entry A).[20] The (*R*,*R*)-tartrate and the *d*-diisopinocampheyl ligands in reagents **33c** and **33b** were unable to overcome the inherent substrate-governed facial selectivity for the Felkin product **34**. The reactions of Garner's aldehyde **36** with diisopinocampheyl (*E*)-3-trimethylsilyl crotylboranes **37a**,**b** appear also to be strongly influenced by substrate control (Figure 10, entry B).[19] In this sequence, the crotylboration reaction is followed by oxidative desilylation to furnish allylic alcohols **38** and **39**. In the mismatched reaction of **36** with **37b**, the Felkin product **38** is favored over the anti-Felkin adduct **39**. However, allylboration reactions of **36** proceed with the expected reagent control.[7] These results, in aggregate, support our indication that one must be extremely cautious in the choice of crotylmetal reagent and nitrogen protecting group to achieve the desired outcome in the crotylation reactions of α-amino aldehyde derivatives.

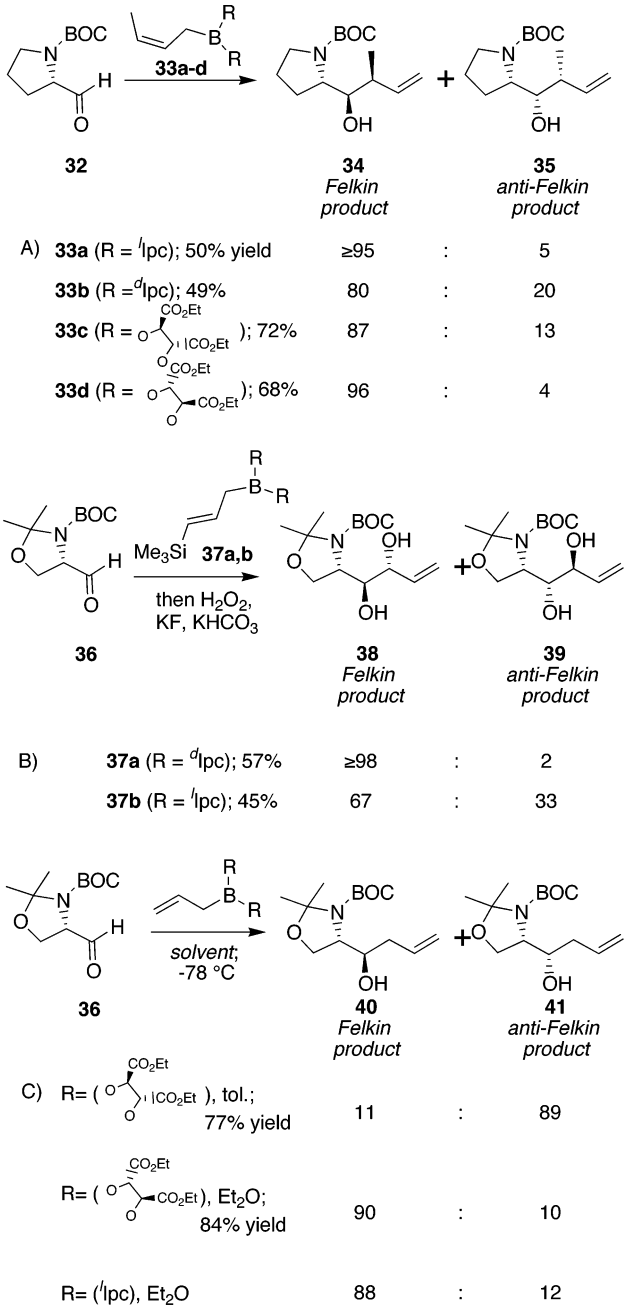

FIGURE 10. Crotylboration reactions of other α-amino aldehydes: entries A,[20] B,[19] and C.[7]

Further studies directed toward the completion of the total synthesis of superstolide A will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for compounds **1**, **3**, **4**, (*R*)- and (*S*)-MTPA esters of **4**, **8**, **9**, **12**−**15**, **17**−**19**, **21**−**24**, **31**, (*R*)- and (*S*)-MTPA esters of **31**; ^{1}H and ^{13}C NMR spectra of **8**, **9**, **12**, **13**, **15**, **23**, (*R*)- and (*S*)-MTPA esters of **4** and **31**; ORTEP plots and crystallographic information files (CIF) for **4** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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