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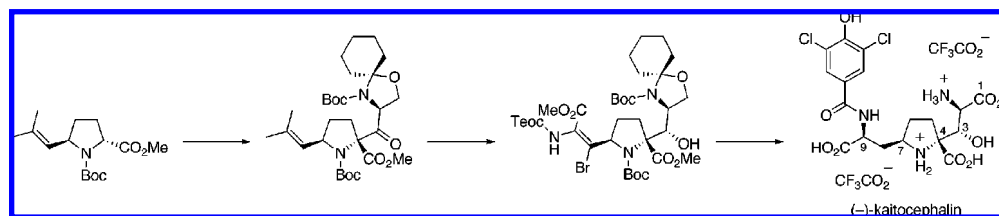
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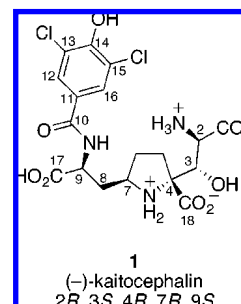
## Stereocontrolled Total Synthesis of (–)-Kaitocephalin

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This paper describes the successful implementation of a stereocontrolled strategy for the total chemical synthesis of the pyrrolidine-based alkaloid (–)-kaitocephalin. This scalable synthetic route profits from the strategic utilization of substrate-controlled manipulations for the iterative installation of the requisite stereogenic centers. The key transformations include a diastereoselective modified Claisen condensation, a chemo- and diastereoselective reduction of a  $\beta$ -keto ester, and the substrate-directed hydrogenation of a dehydroamino ester derivative. During the course of our investigations, an interesting stereocovergent cyclization reaction was discovered for the efficient assembly of the kaitocephalin 2,2,5-trisubstituted pyrrolidine core.

## Introduction

L-Glutamic acid (L-Glu) is recognized as the principle excitatory neurotransmitter in the mammalian central nervous system (CNS) and is involved in numerous important physiological mechanisms, such as fast interneuronal signaling, sensory perception, memory, learning, and synaptic plasticity.<sup>1</sup> Conversely, the overarching physiological significance of L-Glu in normal CNS function is counterbalanced by a number of pathological processes.<sup>2</sup> Thus, in addition to the central role of ionotropic glutamate receptor (iGluR) activation in normal neuronal function, excessive stimulation of the iGluRs by either L-Glu itself or by any of a large number of iGluR agonists can trigger a cascade of detrimental cellular events that ultimately lead to neuronal injury or death. This abnormal response to iGluR activation, known as excitotoxicity, is postulated to play a role in a variety of neurodegenerative disorders including epilepsy,<sup>3a–c</sup> Parkinson's disease,<sup>3a,c</sup> and Alzheimer's disease.<sup>3a,c</sup> Because injury to neurons in many such neurological disorders may be caused, at least in part, by overstimulation of the iGluRs,<sup>3</sup> agents capable of attenuating receptor activity have



**FIGURE 1.** Structure of (–)-kaitocephalin.

attracted considerable interest as potential neuroprotectants. The possibility that selective antagonists of the iGluRs may ameliorate the destructive effects of glutamate excitotoxicity has motivated extensive research efforts by both academic and pharmaceutical institutions to identify novel iGluR antagonists capable of therapeutic intervention for certain neuropathologies.<sup>3c,4</sup>

Our own interest in this area was stimulated by the discovery of the first naturally occurring glutamate receptor antagonist, kaitocephalin (**1**) (Figure 1). In 1997, Shin-ya and co-workers isolated this novel pyrrolidine-based alkaloid from the filamentous fungus *Eupenicillium shearii* PF1191.<sup>5,6</sup> In initial biological screening, kaitocephalin suppressed kainic acid toxicity with a reported EC<sub>50</sub> value of 0.68  $\mu$ M at 500  $\mu$ M concentration of

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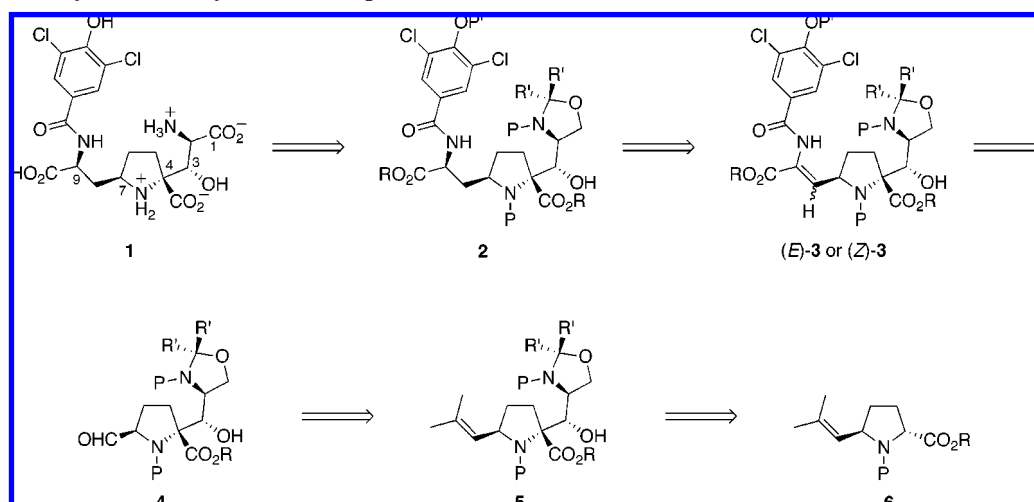
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**SCHEME 1. Retrosynthetic Analysis of Kaitocephalin (1)**



the agonist kainic acid.<sup>5a</sup> Analogously, when **1** was tested for antagonist activity against  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), an EC<sub>50</sub> value of 0.60  $\mu$ M was reported at 500  $\mu$ M/50  $\mu$ M concentration of AMPA/cyclothiazide.<sup>5a</sup> Thus, as the first naturally occurring iGluR antagonist, **1** is a potential lead compound for the development of therapeutic agents to treat neurological diseases caused by glutamate excitotoxicity. In that regard, a better understanding of the origin of kaitocephalin's antagonist activity at the iGluRs would require not only ample quantities of kaitocephalin for further physiological investigations but also the biological evaluation of various kaitocephalin analogues to develop structure–activity relationships (SAR) and elucidate the structural features that contribute to iGluR antagonism. These needs coupled with limited availability from natural and synthetic sources motivated us to develop a stereocontrolled total synthesis of (–)-kaitocephalin that also provides scaffolds to be employed later for analog library synthesis.

## Synthesis Plan

Both the unusual structure and unique biological profile of kaitocephalin make this natural product a compelling target for further study. Since the elucidation of its structure,<sup>6</sup> the Kitahara,<sup>7</sup> Ohfuné,<sup>8</sup> and Ma<sup>9</sup> research groups have independently reported total syntheses of **1** that illustrate a multiplicity of noteworthy synthetic challenges in a relatively simple natural product, including the formation of the substituted pyrrolidine core, the installation of the tetrasubstituted C4 stereocenter, the stereoselective introduction of the C3 secondary alcohol stereocenter, and the efficient incorporation of the C2 and C9 amino acid moieties.

Our goal was to implement a concise, scalable, and stereo-controlled total synthesis of **1** via a general strategy that would

elaborate bidirectionally on an enantiomerically pure substituted pyrrolidine scaffold. Retrosynthetic simplification of **1** first exposes saturated amino ester **2**. In the forward synthetic sense, the construction of **1** would be accomplished by hydrolytic cleavage of the *N,O*-acetal of **2**, followed by chemoselective oxidation of the resultant C1 primary alcohol, and finally deprotection of the protecting groups (Scheme 1). In turn, we planned to install the C9 stereocenter of amino ester **2** from aldehyde **4** by a sequential Horner–Wadsworth–Emmons olefination and hydrogenation of the resultant dehydroamino ester (*E*)-**3** or (*Z*)-**3**. Aldehyde **4** could be prepared from the oxidative cleavage of the olefinated pyrrolidine **5**, which contains the requisite C2, C3, C4, and C7 stereocenters. Further disconnection of pyrrolidine **5** suggests that the C4-tetrasubstituted center and the C3 secondary alcohol center could be accessed from an aldol reaction between a metal enolate derived from pyrrolidine ester **6** and an appropriate chiral aldehyde. Alternatively, a stepwise protocol involving the *C*-acylation of the enolate derived from **6** followed by a stereoselective reduction of the resultant  $\beta$ -keto ester could also allow entry to pyrrolidine **5**. The 2,5-disubstituted pyrrolidine ester (**6**) would most obviously be prepared from the amino acid chiral pool (e.g., from pyroglutamate or a related structure).

Aside from the general synthetic challenges posed by the dense array of stereocenters, we viewed two specific issues as the most challenging requirements in developing an efficient approach: (1) the olefination of pyrrolidine aldehyde **4** and diastereoselective reduction of the resultant dehydroamino ester (*E*)-**3** or (*Z*)-**3** to install the C9 stereocenter and (2) the stereochemical outcome of the proposed aldol reaction between Garner's aldehyde and the 2,5-disubstituted pyrrolidine ester **6**, in which the possible occurrence of complicated double stereodifferentiation could undermine our prediction that the desired diastereoselectivity would result from steric influence of the vinyl substituent.

## Results and Discussion

**Synthesis of 2,5-Disubstituted Pyrrolidine Ester.** The synthesis began with the exploration of methods for the construction of the *trans*-2,5-disubstituted pyrrolidine ring **6**.<sup>10</sup> The addition of organocopper reagents to the chiral *N*-acyliminium ion derived from (*R*)-pyroglutamic acid (**7**) reportedly provides an efficient means of synthesizing pure *trans*-2,5-disubstituted pyrrolidines,<sup>10,11a–f</sup> an approach that in this case

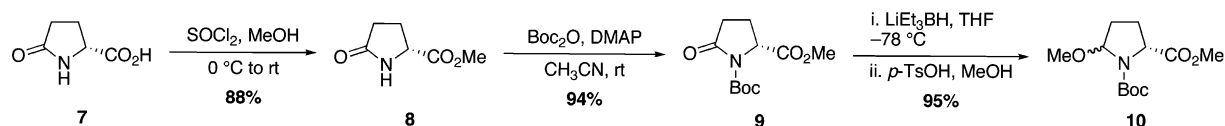
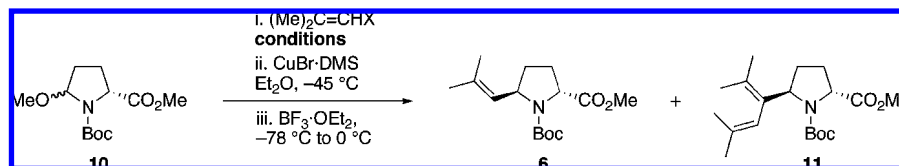
(6) The initial absolute stereochemical assignment of kaitocephalin was based on chemical derivatization and NMR studies, which led to the misassignment of the C2 center as C2-(*S*) (see ref 5b). This misassignment was later corrected through the first total synthesis of kaitocephalin by Kitahara and co-workers and established as C2-(*R*) (see ref 7).

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(9) Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706–9707. The synthesis of the C2-(*S*) isomer of **1** was reported.

## SCHEME 2. Preparation of Aminoal 10

TABLE 1. *N*-Acylliminium Approach to the Formation of Pyrrolidine 6

| entry | X  | conditions   | 6                                      | 11                                     |
|-------|----|--|--|--|
|       |    |  | yield (%), dr (trans/cis) <sup>a</sup> | yield (%), dr (trans/cis) <sup>a</sup> |
| 1     | Br | <i>t</i> -BuLi, THF –78 °C to 0 °C                       | 45 (>20:1)                             | 20                                     |
| 2     | Br | Li(0) (5% Na content) Et <sub>2</sub> O, –10 °C to 0 °C  | 45 (>20:1)                             | 18                                     |
| 3     | I  | <i>t</i> -BuLi, THF –78 °C to 0 °C                       | 89 (8:1)                               |  |
| 4     | Br | Mg(0), THF rt to 60 °C                                   | 69–78 (15:1–20:1)                      | 5–10                                   |
| 5     |    | commercially available 2-methylpropenylmagnesium bromide | 50–86 (15:1–20:1)                      | 0–30                                   |

<sup>a</sup> Trans/cis ratios were determined by <sup>1</sup>H NMR spectroscopic analysis of crude reaction mixtures.

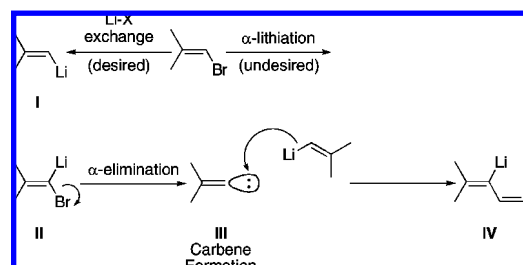
required formation of aminoal **10**. Accordingly, esterification of (*R*)-pyroglutamic acid (**7**) using catalytic SOCl<sub>2</sub> in MeOH provided lactam ester **8** in 88% yield (Scheme 2).<sup>12</sup> Protection of the lactam nitrogen of **8** was carried out using Boc<sub>2</sub>O and DMAP to furnish imide **9** in 94% yield after crystallization.<sup>13</sup> Chemoselective reduction of **9** was accomplished by careful addition of lithium triethylborohydride in THF at –78 °C.<sup>11a,14</sup> The resultant hemiaminal was immediately subjected to catalytic *p*-TsOH in MeOH to afford *N,O*-acetal **10** as a 1:1 mixture of diastereomers in 95% yield.<sup>11a</sup> Aminoal **10** was prepared on a 25 g scale in 79% yield over four steps (starting from **7**) and could be stored indefinitely at –20 °C with negligible hydrolysis.

The successful preparation of aminoal **10** led next to investigations into the addition of organocopper reagents to the corresponding chiral *N*-acylliminium ion (Table 1). Treatment of 1-bromo-2-methylpropene with either *t*-BuLi or Li(0) metal, followed by transmetalation with CuBr·DMS and addition of BF<sub>3</sub>·OEt<sub>2</sub> and **10**, provided the trans-2,5-disubstituted pyrrolidine **6** in 45% yield as a >20:1 diastereomeric mixture (entry 1–2). In addition to the isolation of the desired pyrrolidine product **6**, diene-incorporated trans-2,5-disubstituted pyrrolidine product

**11** was also produced in 20% yield.<sup>10,15–17</sup> In an effort to improve on the yield of this organocuprate, vinylation coupled with the unanticipated formation of diene **11** prompted us to investigate alternative metal–halogen exchange conditions. We rationalized that employing a vinyl iodide for the lithium–halogen exchange should ultimately prevent the formation of **11**.<sup>18</sup> Subjection of iodo-2-methylpropene<sup>19</sup> to the lithium–halogen exchange conditions followed by copper-mediated transmetalation and finally addition of BF<sub>3</sub>·OEt<sub>2</sub> and **10** afforded **6** in a trans/cis diastereomeric ratio of 8:1 in 89% yield (entry 3). As expected under these conditions, the formation of the diene-incorporated pyrrolidine **11** was suppressed; however, the erosion in diastereoselection from 20:1 to 8:1 was considered unsatisfactory for our synthesis, thus necessitating further examination of this key transformation.

After exhaustive screening, it was found that the optimal conditions for the diastereoselective synthesis of pyrrolidine **6** utilized the 2-methylpropenylmagnesium bromide, derived from 1-bromo-2-methylpropene (entry 4). Transmetalation of the Grignard reagent with CuBr·DMS and sequential addition of

(15) The formation of **11** was speculated to arise as a result of competing α-lithiation of 1-bromo-2-methylpropene, leading to the formation of a reactive carbene intermediate **III** (see below). Addition of another 2-methylpropenyl lithium species to the carbene intermediate would produce the lithiated diene nucleophile. Transmetalation with CuBr·DMS followed by sequential treatment with BF<sub>3</sub>·OEt<sub>2</sub> and aminoal **10** would result in the formation of side product **11**.



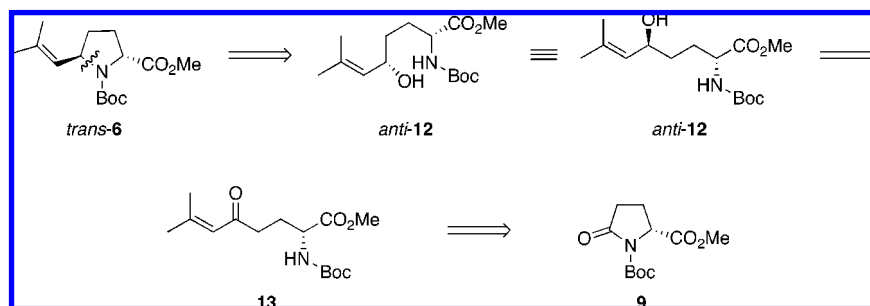
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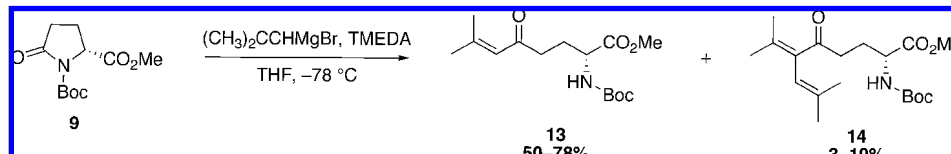
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SCHEME 3. Retrosynthetic Analysis for the Cyclization Reaction of *anti*-12

## SCHEME 4. Chemoselective Ring Opening of Imide 9



$\text{BF}_3 \cdot \text{OEt}_2$  and *N,O*-acetal 10 successfully produced the desired pyrrolidine 6 in 69–78% with diastereomeric ratios ranging from 15:1 to 20:1. The formation of side product 11 was minimized under these conditions to 5–10% yield.<sup>20</sup>

**Stereoconvergent Cyclization Reaction for the Synthesis of 6.** Although the cuprate procedure gave reasonable yields, there were several limitations that prompted us to continue searching for a more satisfactory process. First, the formation of the dienyl pyrrolidine 11 could not be completely suppressed, and the separation of desired pyrrolidine 6 from 11 by silica gel chromatography required multiple chromatographic runs to obtain pure samples of 6. Second, several operational difficulties were encountered during the generation of the Grignard reagent on large scale: 2-methylpropenylmagnesium bromide had a

propensity to precipitate from the solution, and the resultant heterogeneous mixture could not be transferred efficiently via cannula. Consequently, the Grignard mixture required relatively high dilution in THF before a homogeneous solution could be attained, resulting in disproportionately large reaction volumes. Last, excessive quantities of  $\text{CuBr} \cdot \text{DMS}$ , Grignard reagent, and  $\text{BF}_3 \cdot \text{OEt}_2$  (at least 3 equiv of each reagent) were required to obtain diastereoselectivities of >20:1. The copious amounts of  $\text{CuBr} \cdot \text{DMS}$  produced considerable quantities of copper waste and limited the workable scale of this transformation. Ultimately, these constraints were considered to be sufficiently unsatisfactory that an alternative method for the synthesis of the pyrrolidine core was pursued.

In an alternative route that ultimately provided not only a workable solution but also an interesting surprise, the pyrrolidine 6 was envisioned to arise from allylic alcohol *anti*-12 via an  $\text{S}_\text{N}2$  cyclization of the nitrogen atom onto an appropriately activated allylic alcohol (Scheme 3). The cyclization substrate, *anti*-12, would derive from imide 9 by sequential ring opening and stereoselective reduction of enone 13. The possibly delicate nature of the allylic substitution in *anti*-12 would require that alcohol activation and ring formation occur under mild conditions in order to preserve the stereochemical integrity of the hydroxyl moiety, which we assumed would be relayed stereospecifically during the cyclization event to give the desired *trans* diastereomer.

This cyclization approach to give the pyrrolidine 6 commenced with the chemoselective ring opening of imide 9 employing 2-methylpropenylmagnesium bromide in the presence of TMEDA to furnish enone 13 in 50–78% yield (Scheme 4).<sup>21</sup> The remainder of the mass consisted of dienyl-enone 14 and the recovered starting material (9). Next, the stereoselective 1,2-reduction was explored to prepare the requisite allylic alcohol *anti*-12 (Table 2). Initial investigations examined the diastereoselective outcome of the reduction of enone 13 using achiral reagents. Thus, treatment of enone 13 under Luche conditions,<sup>22</sup>  $\text{NaBH}_4/\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (entry 1), produced an equimolar mixture of allylic alcohols *anti*-12 and *syn*-12, respectively. The anticipated lack of stereoselectivity observed in the substrate-

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(20) Although 2-methylpropenylmagnesium bromide is commercially available as a 0.5 M solution in THF, the significance of the efficient generation of the Grignard reagent from the corresponding vinyl bromide is underscored by the inconsistent results observed when commercially available Grignard reagent was used in the organocuprate-mediated alkenylation. With commercially available 2-methylpropenylmagnesium bromide, depending on the batch number, pyrrolidine 9 was furnished in yields varying from 50–86%, and the dienyl pyrrolidine 12 was produced in 0–30% yield, albeit with little effect on diastereoselectivity (see Table 1, entry 5). Thus, optimized conditions for this transformation required the generation of the Grignard to deliver pyrrolidine 9 in 69–78% yield with minimal formation of the dienyl pyrrolidine 12.

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TABLE 2. Stereoselective Reduction of Enone **13**

| entry | conditions   | dr (anti:syn) <sup>a</sup> of <b>12</b> | yield (%) |
|-------|--|---|-----------|
| 1     | NaBH <sub>4</sub> , CeCl <sub>3</sub> ·7H <sub>2</sub> O, MeOH, –78 °C               | 1:1                                     | 88        |
| 2     | BH <sub>3</sub> ·THF (1.00 equiv) ( <i>R</i> )-Me-CBS (1.20 equiv) THF, –78 °C to rt | 15:1                                    | 72        |
| 3     | BH <sub>3</sub> ·THF (1.00 equiv) ( <i>S</i> )-Me-CBS (1.20 equiv) THF, –78 °C to rt | 1:33                                    | 41        |

<sup>a</sup> Anti/syn ratios were determined by normal-phase analytical HPLC of crude reaction mixtures.

TABLE 3. Cyclization Reaction of Allylic Alcohol *anti*-**12** with Ph<sub>3</sub>P, I<sub>2</sub>, and Imidazole

| entry | conditions  | dr (anti:syn) of <b>12</b> | yield (%) of <b>6</b> | dr (trans/cis) <sup>a</sup> of <b>6</b> | yield (%) of <b>15</b> |
|-------|---|----------------------------|-----------------------|---|------------------------|
| 1     | Ph <sub>3</sub> P (1.10 equiv), I <sub>2</sub> (1.12), imid (2.11 equiv), THF –78 °C to rt, 16–24 h | 14:1                       | 50                    | 22:1                                    |                        |
| 2     | Ph <sub>3</sub> P (1.24 equiv), I <sub>2</sub> (1.23), imid (2.63 equiv), THF –78 °C to rt, 24 h    | 4:1                        | 50                    | 26:1                                    |                        |
| 3     | Ph <sub>3</sub> P (2.50 equiv), I <sub>2</sub> (2.57), imid (5.10 equiv), THF –78 °C to rt, 16 h    | 4:1                        | 94                    | 24:1                                    |                        |
| 4     | Ph <sub>3</sub> P (2.00 equiv), I <sub>2</sub> (2.00), imid (5.00 equiv), THF –78 °C to rt, 24 h    | 1:1                        | 74                    | 14:1                                    | 3–4                    |
| 5     | Ph <sub>3</sub> P (1.30 equiv), I <sub>2</sub> (1.00), imid (1.69 equiv), THF 0 °C to rt, 16–24 h   | 1:33                       | 50                    | 10:1                                    | 2–5                    |
| 6     | Ph <sub>3</sub> P (2.00 equiv), I <sub>2</sub> (2.00), imid (4.00 equiv), THF 0 °C to rt, 24 h      | 1:5                        | 93                    | 12:1                                    |                        |

<sup>a</sup> Trans/cis ratios were determined by normal-phase analytical HPLC of crude reaction mixtures.

directed reduction of enone **14** was corrected by the use of chiral reagents to enforce the desired diastereofacial preference in the ketone reduction, and ultimately, use of the Corey–Bakshi–Shibata (CBS) reagent provided superior diastereoselection for the reduction of **13**.<sup>23</sup> It was determined, however, that optimal levels of diastereoselectivity required the use of stoichiometric quantities of CBS reagent; for example, the reduction of enone **13** necessitated the use of 120 mol % of (*R*)-Me-CBS, and BH<sub>3</sub>·THF furnished allylic alcohol *anti*-**12** in 72% yield (dr anti/syn = 15:1) (entry 2).<sup>24</sup> The reduction of enone **13** with the enantiomeric (*S*)-Me-CBS reagent afforded the expected stereocomplementary product *syn*-**12** (entry 3), confirming that lack of any significant stereochemical influence of the relatively remote extant stereogenic center under these conditions.

Having successfully established conditions for the diastereoselective formation of allylic alcohol *anti*-**12** (see Table 2), the key cyclization reaction to form *trans*-**6** was addressed (Table 3). After considerable experimentation, we observed that the cyclization of allylic alcohol *anti*-**12** proceeded smoothly in the presence of Ph<sub>3</sub>P, I<sub>2</sub>, and imidazole to afford the desired pyrrolidine *trans*-**6** in 50% yield (entry 1). HPLC analysis of the pyrrolidine product mixture, however, revealed an unexpected enhancement—small but reproducible—in the diastereomeric ratio; that is, exposure of a 14:1 (anti-/syn-) diastereomeric mixture of allylic alcohol **12** to Ph<sub>3</sub>P, I<sub>2</sub>, and imidazole produced pyrrolidine *trans*-**6** as a 22:1 diastereomeric mixture (entry 1) instead of the anticipated 14:1 ratio of products.

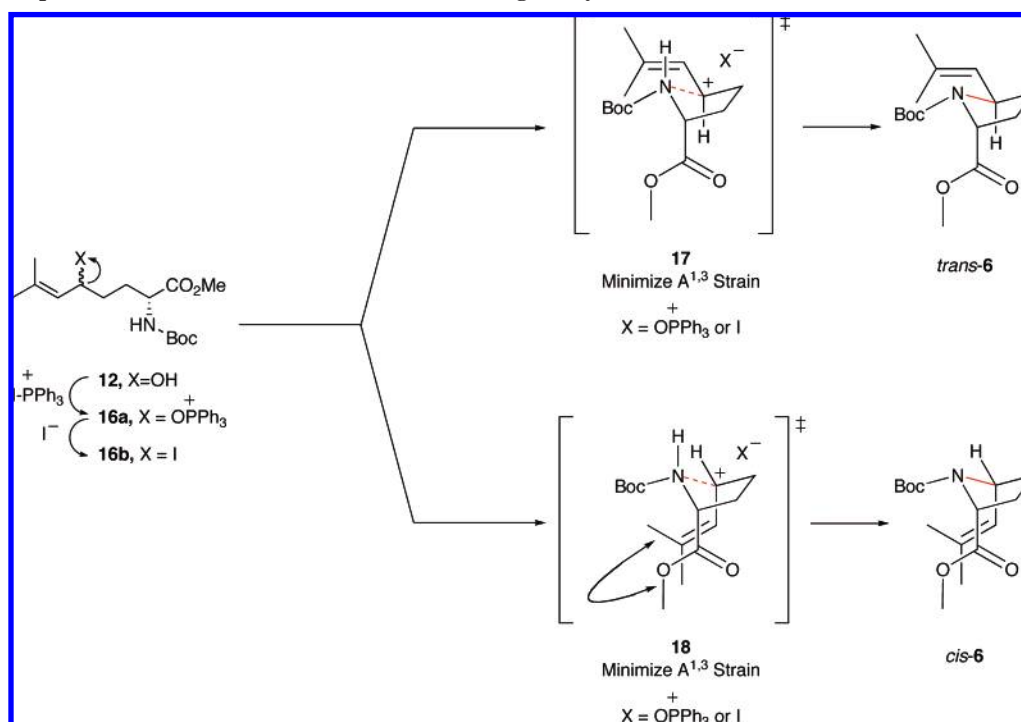
Although we might have rationalized this small difference as due to a minor fluctuation in reaction conditions and moved on, we wondered if it might instead be signaling something more significant. We therefore checked whether this enhancement in diastereoselectivity occurred with other reactant ratios and found that when a 4:1 (anti-/syn-) diastereomeric mixture of **12** was subjected to identical reaction conditions (entry 2) the reaction produced **6** with a similar enhancement in diastereoselectivity to give a 26:1 mixture of *trans*- and *cis*-diastereomers in 50% combined yield. Under optimized conditions employing 2.5 equiv of I<sub>2</sub>, 2.5 equiv of Ph<sub>3</sub>P, and 5 equiv of imidazole, the cyclization of a 4:1 (anti-/syn-) mixture of allylic alcohols **12** afforded **6** as a 24:1 (*trans*-/*cis*-) mixture of diastereomers in 94% combined yield (entry 3).<sup>25</sup>

With our interest now stimulated, mixtures of starting allylic alcohol favoring the diastereomeric (“wrong”) substrate (*syn*-**12**) were tested under the same reaction conditions (Table 3, entries 5 and 6). Interestingly, we found that treatment of a 1:5 (anti-/syn-) diastereomeric mixture of **12** with Ph<sub>3</sub>P, I<sub>2</sub>, and imidazole still provided predominantly *trans*-**6** as a 12:1 (*trans*-/*cis*-) mixture of diastereomers (93% combined yield). Clearly, the cyclization of allylic alcohol *syn*-**12** was proceeding selectively but with *net retention* of stereochemistry; that is, allylic alcohol *syn*-**12** cyclized to furnish predominantly the pyrrolidine *trans*-**6**, the same product as produced in the

(23) For an excellent review on the CBS reagents, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(24) The stereochemical outcome of the reduction of **13** using (*R*)-Me-CBS reagent was inferred based on literature precedent: Li, A.; Yue, G.; Li, Y.; Pan, X.; Yang, T.-K. *Tetrahedron: Asymmetry* **2003**, *14*, 75–78.

(25) It should be noted that the potential for the imidazole-mediated epimerization at the C2 α-center of *cis*-**6** to produce the *ent-trans*-**6** was not observed. Regardless of the diastereomeric ratio of the starting allylic alcohol **12**, the cyclization event produced *trans*-**6** with no significant degradation in the optical purity. The optical rotation measured for *trans*-**6**, produce during the stereoconvergent cyclization strategy, was similar in sign and magnitude to that produced in the organocuprate reaction.

SCHEME 5. Proposed Mechanistic Rationale for Stereoconvergent Cyclization of **12**

cyclization of the diastereomeric allylic alcohol precursor (*anti*-**12**). Thus, both the allylic alcohol diastereomers cyclize to produce pyrrolidine product ratios enhanced in the *trans* isomer; the cyclization of *anti*-**12** proceeds with *inversion* of configuration with respect to the alcohol stereocenter, while cyclization of *syn*-**12** proceeds with *retention* of configuration.

On the basis of these results, it was now obvious that despite the demonstrated lack of a directing effect by the protected amino group in a kinetically controlled reduction to the precursor alcohol, we had stumbled upon a more subtle mechanism of substrate-controlled diastereoselectivity in the subsequent cyclization that renders the “chiral reduction” unnecessary.<sup>26</sup> Thus, treatment of a 1:1 diastereomeric mixture of allylic alcohols **12** with 2 equiv of  $\text{Ph}_3\text{P}$ ,  $\text{I}_2$ , and 5 equiv of imidazole in THF furnished the desired 2,5-disubstituted pyrrolidine (*trans*-**6**) as a 14:1 (*trans*–/*cis*–) mixture of diastereomers in 74% yield (entry 4). This simple procedure obviated the need for stoichiometric quantities of a chiral reducing agent to establish the stereochemical configuration of the allylic alcohol and simply relies on substrate control for the formation of *trans*-**6**, which in turn greatly expedites synthetic access to the pyrrolidine core of kaitocephalin.

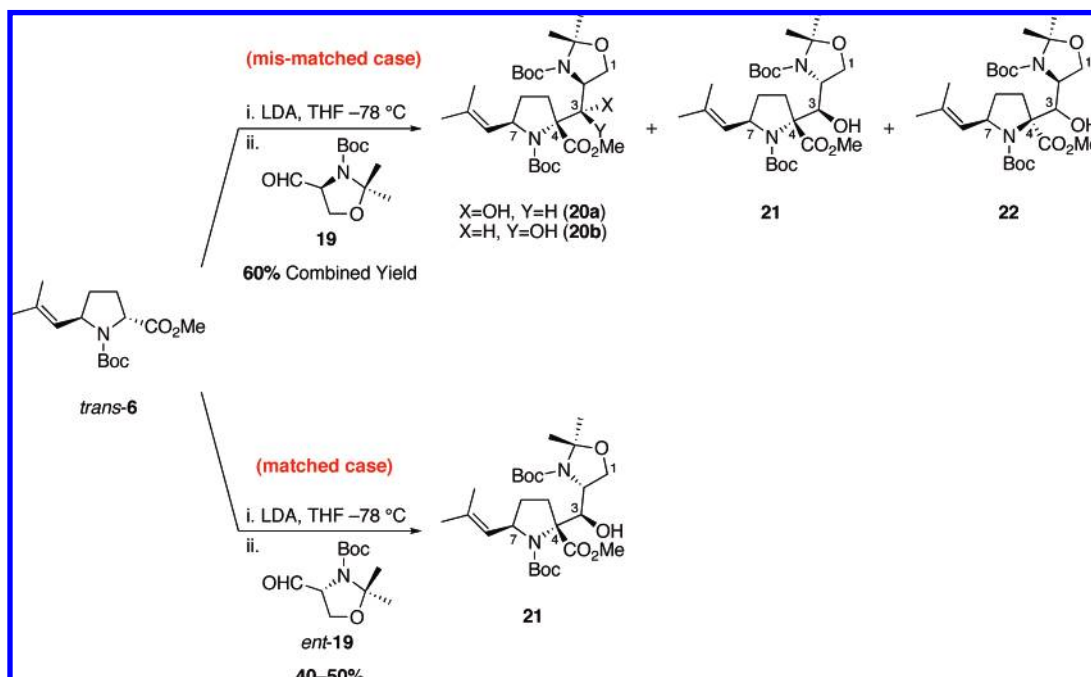
Although an extensive mechanistic analysis has not been performed on this interesting stereoselective cyclization reaction, the intriguing and useful result may be simply rationalized by ring closure in a conformation that minimizes allylic strain in one of two alternative transition states (Scheme 5). The cyclization is initiated by activation of both *anti*- and *syn*-**12** with iodotriphenylphosphonium iodide to give the activated

alcohol **16a**. Ring closure by attack of the weakly nucleophilic carbamate nitrogen would be facilitated by carbocation-like transition states **17** or **18** resulting from loss of the triphenylphosphine oxide leaving group from **16a**, with free rotation in the resultant carbocation giving rise to several possible transition state geometries. It is also possible that the iodide from the reagent displaces the triphenylphosphine oxide from **16a** with inversion (and even subsequently another iodide, resulting in multiple inversions) and that it is the resultant allylic iodide **16b**, or the carbocation derived from it, that undergoes cyclization, again via the transition states shown. Either way, the stereochemistry of the starting alcohol is lost (by carbocation formation or multiple inversions), and thus, the stereochemical outcome of the reaction would not be determined by the stereochemistry of the alcohol starting material as originally supposed, but instead by the relative energies of the respective cyclic transition states (**17** and **18**), which in turn are governed by well-established stereoelectronic and conformational factors.<sup>27</sup> Specifically, in this case, **17** would be energetically preferred over **18** because of the indicated steric strain in the latter, and thus, *trans*-**6** is the preferred product formed from either *anti*- or *syn*-**12** under these reaction conditions.

**Establishing the Tetrasubstituted C4 Stereocenter.** With a viable synthesis of the requisite pyrrolidine core (*trans*-**6**) in hand, attention next focused on constructing the tetrasubstituted C4 stereocenter of kaitocephalin. A lithium enolate aldol reaction between the *trans*-**6** and (*S*)-Garner's aldehyde<sup>28</sup> (**19**) was envisioned for the simultaneous introduction of the C4 and C3 stereocenters of kaitocephalin. To that end, *trans*-**6** was

(26) In a related system, utilizing  $\text{MsCl}$  and  $\text{Et}_3\text{N}$  for the cyclization of a 1:1 mixture of allylic alcohols reported similar enhancement for the formation of a *trans*-pyrrolidine isomer, albeit with much lower diastereomeric ratios (2:1): (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, 65, 2163–2171. (b) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, 29, 329–332. (c) Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091–2094.

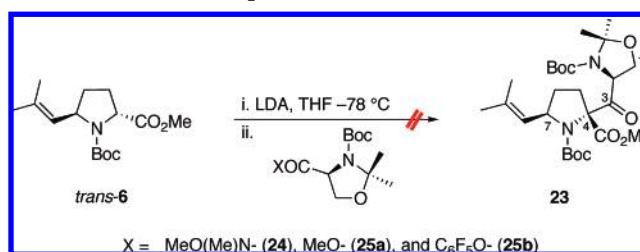
(27) (a) The stereoelectronic factor that contributes to **17** and **18** include the parallel alignment of the  $\sigma_{\text{C-X}}$  bond of the leaving group with the  $\pi$ -system of the double bond. The conformational factor that contributes to **17** and **18** involves minimizing allylic strain ( $A^{1,3}$  strain) between the methyl substituent, occupying the (*Z*)-position on the double bond, and the allylic center, where the H-atom is placed in plane. (b) For an excellent review on allylic strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1841–1860.

SCHEME 6. Aldol Reaction of Pyrrolidine *trans*-6 with Garner's Aldehyde

treated with LDA at  $-78\text{ }^{\circ}\text{C}$ , followed by the addition of (*S*)-Garner's aldehyde (**19**) (Scheme 6).  $^1\text{H}$  NMR analysis of the unpurified reaction mixture revealed a complex mixture of four aldol adducts in a ratio of 2:2:1:1 based on comparison of the integration values for the vinyl proton; in addition, unreacted aldehyde **19** and a mixture of 2,5-disubstituted pyrrolidines, *trans*-6 and C2-*epi*-6, were also detected (Scheme 6).<sup>29</sup>

The stereochemical outcome of the aldol reaction between pyrrolidine ester *trans*-6 and (*S*)-Garner's aldehyde (**19**) clearly suggested that the desired aldol reaction was a case of mismatched double stereodifferentiation. To confirm this assertion, an aldol reaction between *trans*-6 and (*R*)-Garner's aldehyde (*ent*-**19**) was performed; indeed, this reaction provided one diastereomer of the aldol product **21** in an unoptimized yield of 40%, indicating a matched double stereodifferentiation (Scheme 6). The unfortunate mismatched stereochemical outcome of the key aldol reaction between *trans*-6 and aldehyde **19** necessitated a revision of our strategy for the formation of the C3 and C4 stereocenters.

**C-Acylation Chemistry with *N*-Acylimidazole.** An alternative approach to the kaitocephalin intermediate **20a** simply would generate the C4 and C3 centers sequentially: first, C-acylation of the ester enolate derived from *trans*-6 with a serine-derived electrophilic acylating agent to form the C4 stereocenter and, second, a diastereoselective reduction of the resultant  $\beta$ -keto ester **23** to install the C3 secondary alcohol. To implement this plan, various serine-derived electrophiles for

SCHEME 7. Unsuccessful C-Acylation of *trans*-6 with Serine-Derived Electrophiles

the C-acylation of *trans*-6 were surveyed (Scheme 7). Unfortunately, addition of Weinreb amide **24**, methyl ester **25a**, or pentafluorophenyl ester **25b** to the lithium enolate of pyrrolidine ester *trans*-6 failed to afford any of the desired C-acylation product (**23**).

Uncertain at this point whether the lack of success was due to kinetic or thermodynamic problems, we sought other leaving groups in the modified Claisen condensation for this key bond construction. The utility of *N*-acylimidazoles for the C-acylation of enolates, especially in the context of natural product synthesis, has been widely established.<sup>30</sup> To that end, serine-derived *N*-acylimidazole **26** was synthesized from L-serine on scales greater than 20 g and was stable indefinitely when stored under an atmosphere of Ar at  $-20\text{ }^{\circ}\text{C}$  (Scheme 8).

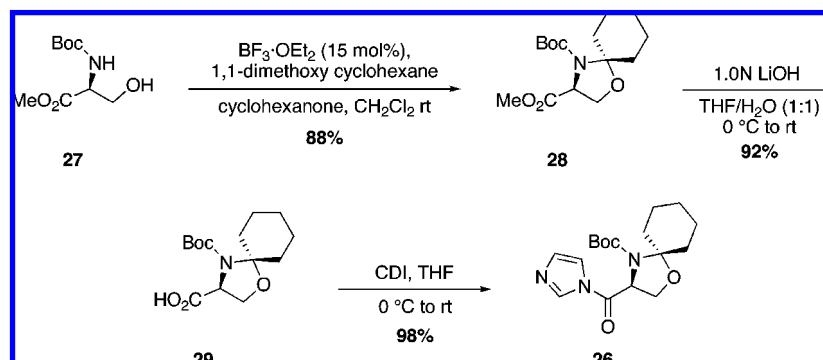
Following the successful preparation of *N*-acylimidazole **26**, the C-acylation of *trans*-6 was conducted by the addition of **26** to a solution of the lithium enolate derived from pyrrolidine ester *trans*-6.<sup>31</sup>  $^1\text{H}$  NMR and normal-phase HPLC analysis of the crude reaction mixture indicated that the  $\beta$ -keto ester **30**

(28) (*S*)-Garner's aldehyde was synthesized according to the procedure reported by Dondoni: Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64–77. For other syntheses of (*S*)-Garner's aldehyde, see: Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18–28. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361–2364.

(29) Chiral HPLC analysis of the unreacted (*S*)-Garner's aldehyde starting material indicated that **19** was formed in high enantiomeric purity. The formation of aldol adduct **21**, therefore, suggested that some epimerization of the chiral aldehyde occurred under the basic reaction conditions. This conjecture was confirmed after chiral HPLC analysis of the Garner's aldehyde recovered from the aldol reaction, which revealed significant racemization.

(30) For some examples on the use of *N*-acylimidazoles as C-acylation agents in the context of natural product synthesis see: (a) Ing, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron Lett.* **1998**, *39*, 3509–3512. (b) Hoffmann, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292–2297. (c) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369–2376. (d) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229–4231. (e) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed.* **1979**, *18*, 72–74.

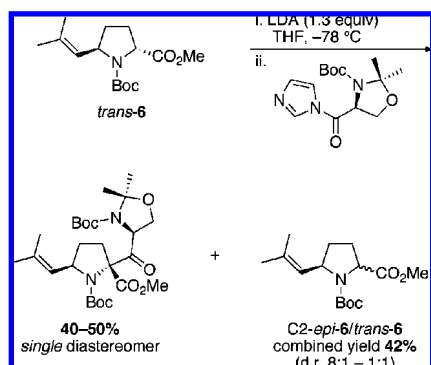


SCHEME 8. Synthesis of *N*-Acylimidazole 26

was generated as a *single* detectable diastereomer in 40–50% yield (Scheme 9). Significantly, the *C*-acylation of *trans*-6 exclusively produced the desired C4-(*R*)-stereocenter; the stereochemistry at the C4 center was determined by NOESY correlation studies and was unambiguously established by a single-crystal X-ray structure of a derivatized late-stage intermediate (*vide infra*).

Although the *C*-acylation of *trans*-6 proceeded in modest yield, this reaction produced no major side products; the remainder of the mass consisted of unreacted starting material and its C2-epimer, *trans*-6 and C2-*epi*-6, respectively, as an inseparable mixture in 42% yield, and the calculated total mass recovery for this transformation was 85–92%. Whether the problem is a thermodynamic issue or one of competing *O*-acylation followed by hydrolysis during workup, this yield could not be improved; however, the starting pyrrolidine *trans*-6 and the epimerized C2-*epi*-6 (presumably produced by nonselective protonation of the corresponding enolate) were easily recovered and re-subjected to the *C*-acylation reaction conditions

(31) Our initial investigation on the *C*-acylation of *trans*-6 involved the use of serine-derived *N,O*-acetonide *N*-acylimidazole (see below). Although this reaction also afforded the desired  $\beta$ -keto ester as a *single* diastereomer in a modest 40–50% yield, the isolation of analytically pure quantities of the desired  $\beta$ -keto ester by silica gel chromatography, however, proved difficult since the unreacted pyrrolidine starting material *trans*-6 and its C2-epimer (C2-*epi*-6) coeluted with the desired *C*-acylated product. The desired product was easily separated from *trans*-6 and C2-*epi*-6 by reversed-phase HPLC; however, HPLC purification on preparatory scales of greater than 100 mg was prohibitive, which compromised synthetic access to useful quantities of this key kaitocephalin intermediate. The purification problem was circumvented by replacing the *N,O*-acetonide with a *N,O*-cyclohexylidene acetal (26).

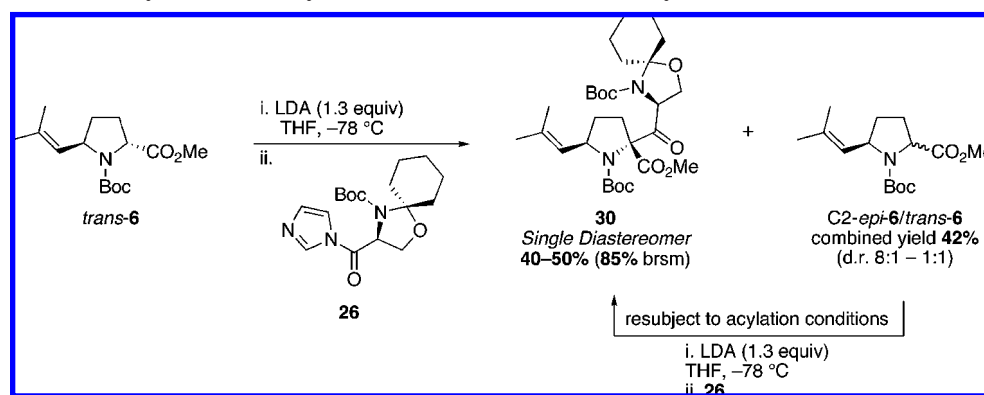
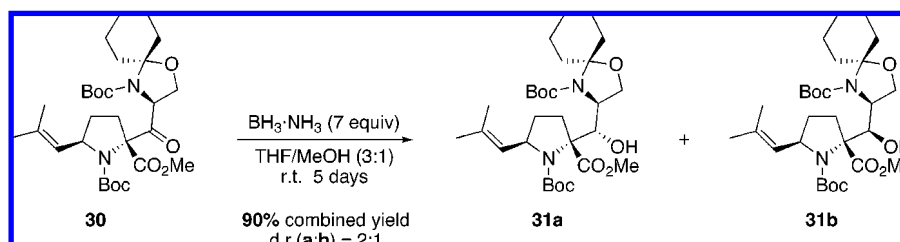


to provide **30** in an additional 40% yield, thereby increasing the overall yield of the Claisen product **30** to ~80% after one recycle. Overall, the diastereoselective Claisen reaction between pyrrolidine *trans*-6 and *N*-acylimidazole **26** reproducibly furnished  $\beta$ -keto ester **30** as a *single* diastereomer in multigram quantities that could be advanced in the synthetic route to kaitocephalin.

**Generation of the C3 Stereocenter: Reduction Studies and Stereochemical Determination.** With the Claisen product successfully prepared and the tetrasubstituted C4 stereocenter secured, we directed our attention to the diastereoselective reduction of the  $\beta$ -keto ester **30** to produce the desired  $\beta$ -hydroxy ester **31a** and establish the C3 secondary alcohol of kaitocephalin (Scheme 10). An investigation of various borane reducing agents (e.g.,  $\text{NaBH}_4$ ,  $\text{Li}(s\text{-Bu})_3\text{BH}$ ,  $\text{Li}(\text{Et})_3\text{BH}$ ,  $\text{BH}_3\cdot\text{THF}$ ,  $\text{BH}_3\cdot\text{DMS}$ ,  $\text{BH}_3\cdot\text{PBU}_3$ ) identified  $\text{BH}_3\cdot\text{NH}_3$  as a highly chemoselective reducing agent: the reduction of  $\beta$ -keto ester **30** with excess  $\text{BH}_3\cdot\text{NH}_3$  (7 equiv) in a solvent mixture of THF/MeOH at ambient temperature afforded a chromatographically inseparable mixture of  $\beta$ -hydroxy ester **31a** and **31b** in >90% combined yield, albeit in modest diastereoselectivity (dr **31a**/**31b** = 2:1). Attempts to improve the diastereoselectivity of this transformation by performing the reaction at lower temperatures (0 °C) proved unproductive, as the  $\text{BH}_3\cdot\text{NH}_3$  reduction of **30** at ambient temperature required unacceptably long reaction times ranging from 4 to 7 days at room temperature.

While the  $\text{BH}_3\cdot\text{NH}_3$  reduction of  $\beta$ -keto ester **30** was highly chemoselective, the 2:1 diastereomeric ratio observed for this reaction was unsatisfactory and mandated further screening of reducing agents. After some experimentation, it was found that the addition of 1 equiv of DIBALH to a solution of **30** in toluene at  $-78$  °C resulted in the formation of  $\beta$ -hydroxy aldehyde **32** as a *single* diastereomer. Although this reduction proceeded with excellent diastereoselectivity at the C3 secondary alcohol, it was plagued by poor chemoselectivity and low conversion that could not be circumvented: the complete consumption of  $\beta$ -keto ester **30** could only be achieved using 3.7 equiv of DIBALH, but this excess also produced  $\beta$ -hydroxy aldehyde **32** (20%), diol **33** (53%), and *N*-Me diol **34** (26%) arising from competitive reduction of the ester and *N*-Boc groups (Scheme 11).

Although chemoselectivity in the reduction of  $\beta$ -keto ester **30** with DIBALH in toluene was poor, it is important to note that the diastereoselection in the production of the C3 secondary alcohol in each isolated product (**32**–**34**) was excellent. We speculated that having performed the reduction in a nonpolar solvent such as toluene might have facilitated the competitive

SCHEME 9. Successful C-Acylation of the Pyrrolidine Ester *trans*-6 with *N*-Acylimidazole 26SCHEME 10. Chemoselective Reduction of 30 with  $\text{BH}_3\cdot\text{NH}_3$ 

reduction of the methyl ester ( $\text{CO}_2\text{R} \rightarrow \text{CHO} \rightarrow \text{CH}_2\text{OH}$ ) and the Boc carbamate ( $\text{Boc} \rightarrow \text{Me}$ ) by favoring coordination to multiple Lewis basic sites in 30 (e.g., O atom of  $\text{CO}_2\text{R}$ ,  $\text{RCOR}'$ , and Boc) and promoting activation of each carbonyl toward reduction. We therefore rationalized that performing the reduction in the presence of Lewis basic solvent, such as THF, might attenuate this promiscuous coordination and minimize the formation of over-reduced products.

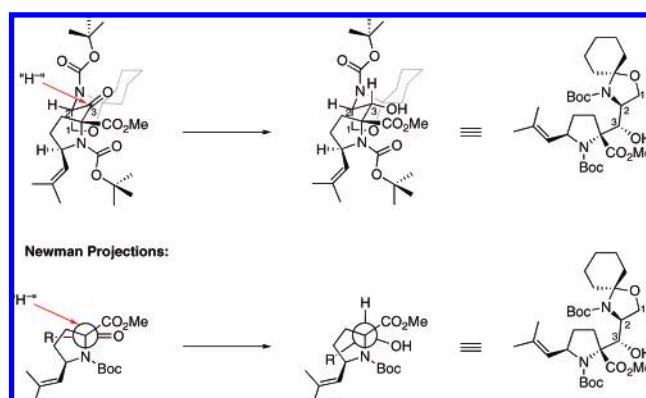
To investigate this possibility,  $\beta$ -keto ester 30 was treated with DIBALH in THF at  $-78^{\circ}\text{C}$ , followed by gradual warming to ambient temperature over 24 h, giving the desired  $\beta$ -hydroxy ester 31a as a *single* diastereomer in 86–93% yield (Scheme 11).<sup>32</sup> Thus, the simple expedient of employing THF as the reaction solvent strikingly increased the chemoselectivity of the transformation while maintaining the desired level of diaste-

reoselection. Neither aldehyde 32 nor *N*-Me diol 34 were detected by  $^1\text{H}$  NMR analysis of crude reaction mixture; the only other product isolated from this reaction was *N*-Boc diol 33, again as a *single* diastereomer, in 10% yield, which could also be easily converted, if desired, into ester 31a by oxidation of the primary alcohol to the carboxylic acid<sup>33,34</sup> and subsequent esterification with trimethylsilyldiazomethane.

The configurations of the reduction products 31a and 31b were determined individually by initial derivatization to the 6-membered *O,O*-benzylidene acetal (Scheme 12), followed by  $^1\text{H}$  NMR evaluation of the coupling constants between the vicinal protons located on the C3 and C2 centers.<sup>35</sup> To that end, an inseparable 2.5:1 mixture of 31a and 31b was treated with 80% aqueous AcOH to effect the hydrolysis of the *N,O*-cyclohexylidene acetal to yield a chromatographically separable mixture of amino diols 35a (65%) and 35b (26%) (Scheme 12a). Exposure of diol 35a to benzaldehyde dimethyl acetal in the presence of catalytic (*S*)-(+)-CSA and 4 Å molecular sieves resulted in the formation of the six-membered *O,O*-benzylidene acetal 36a and the five-membered *N,O*-benzylidene acetal 37 in a ratio of 2:1, respectively (Scheme 12b). Alternatively, addition of catalytic *p*-TsOH to a solution of amino diol 35a and benzaldehyde dimethyl acetal in  $\text{CH}_2\text{Cl}_2$  at room temperature furnished the thermodynamic six-membered *O,O*-benzylidene acetal 36a as a *single* diastereomer in 77% yield. Treatment of amino diol 35b under analogous conditions furnished benzylidene acetal 36b in 48% yield (Scheme 12c).

Due to the presence of carbamate rotamer peaks at room

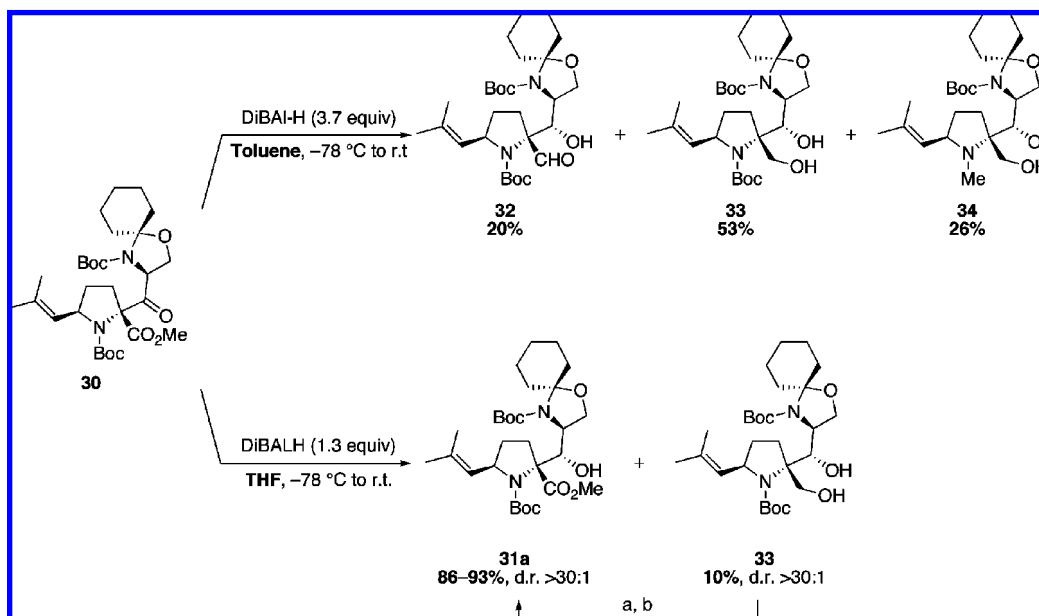
(32) (a) The diastereoselective reduction of  $\beta$ -keto ester 30 was rationalized on the basis of a Felkin–Anh transition-state model shown below, in which the *re*-face of the carbonyl is sterically accessible to a bulky reducing agent, such as DIBALH. As a result, addition of the hydride produced the desired C3-(*S*)-stereochemistry (see below). (b) Anh, N. T. *Top. Curr. Chem.* **1980**, 88, 145.



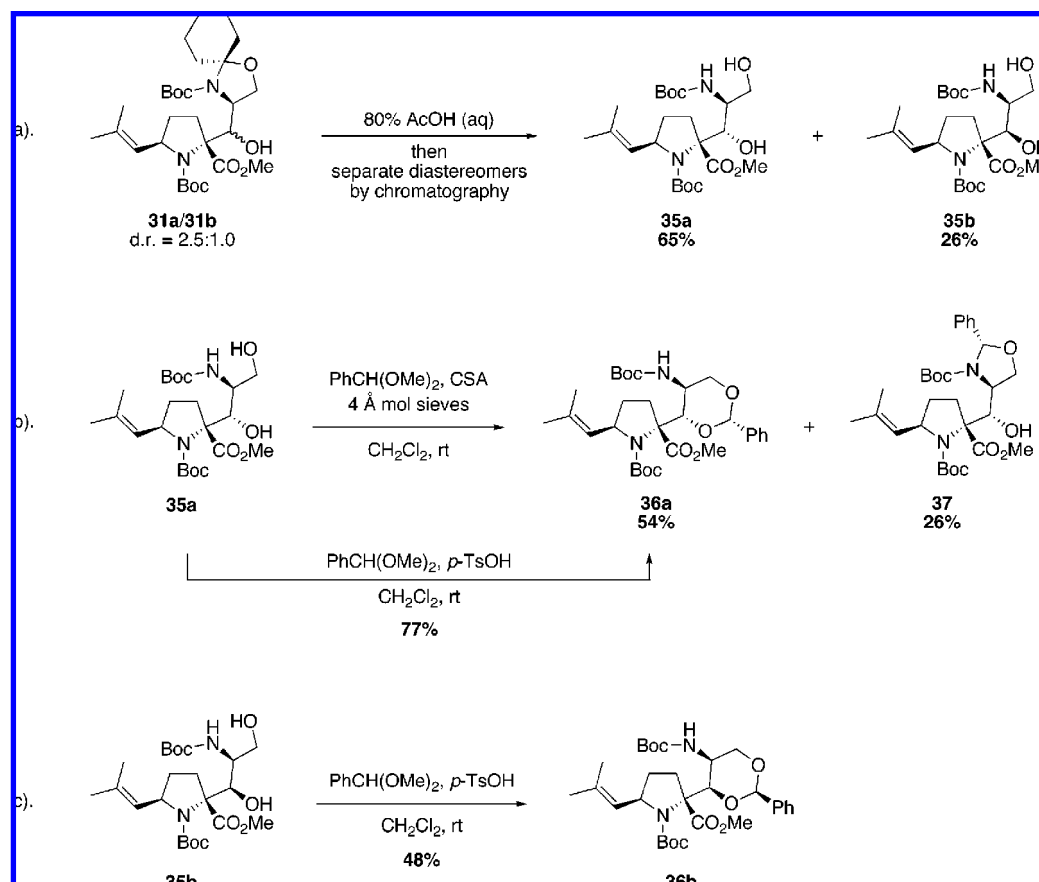
(33) For the use TEMPO and bis-acetoxyiodobenzene in the chemoselective oxidation of primary alcohols to aldehydes, see: De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, 62, 6974–6977.

(34) For the use of sodium chlorite in the oxidation of aldehydes to acids, see: (a) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091–2096. (b) Lindgren, B. O.; Hiltson, T. *Acta Chem. Scand.* **1973**, 27, 888–890.

(35) (a) Herold, P. *Helv. Chim. Acta* **1988**, 71, 354–362. (b) Garner, P. *Tetrahedron Lett.* **1984**, 25, 5855–5858.

SCHEME 11. Reduction of **30** with DIBALH: Solvent Effects<sup>a</sup>

<sup>a</sup> Key: (a) TEMPO (10 mol %), BAIB, CH<sub>2</sub>Cl<sub>2</sub>, rt (78%); (b) NaClO<sub>2</sub>, 2-Me-butene NaH<sub>2</sub>PO<sub>4</sub>, *t*-BuOH/H<sub>2</sub>O (4:1), then TMSCHN<sub>2</sub>, MeOH/EtOAc (90%).

SCHEME 12. Conversion of **31** to Benzylidene Acetals

temperature, <sup>1</sup>H NMR spectroscopic analysis of the benzylidene acetals **36a** and **36b** was performed above the coalescence temperature of 375 K. As depicted in Figure 2, a coupling constant of 9.6 Hz was calculated between the C3 methine proton and the C2 methine proton, H<sub>a</sub> and H<sub>b</sub>, respectively,

clearly representing a trans-diaxial relationship between these protons (nearly 180° alignment based on a vicinal Karplus correlation).<sup>36</sup> The trans-diaxial relationship (between H<sub>a</sub> and H<sub>b</sub>) observed in acetal **36a** ultimately indicated that the cyclohexylidene acetal **31a** has the desired C3-(*S*) stereochem-

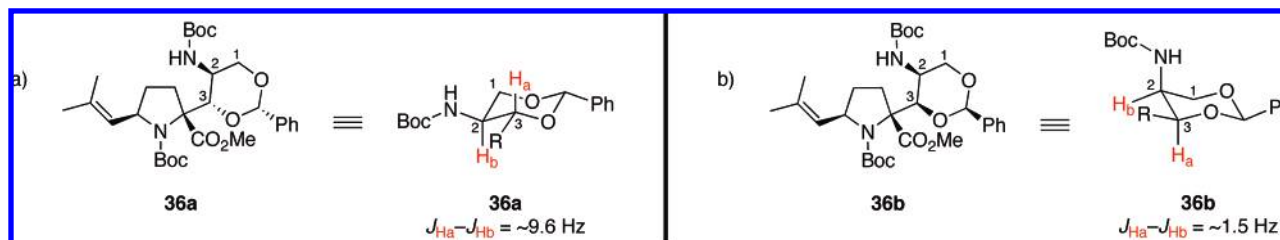


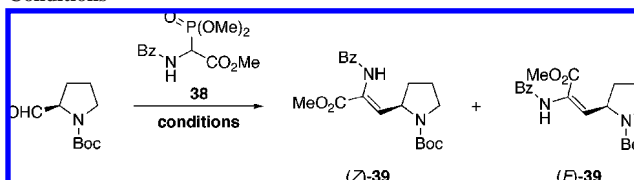
FIGURE 2. Coupling constant analyses of benzylidene acetals **36a** and **36b**.

ical configuration. In contrast to the large coupling constant observed for acetal **36a**, the C3 methine proton and the C2 methine proton of acetal **36b**,  $H_a$  and  $H_b$ , respectively, exhibited  $J = 1.5$  Hz (Figure 2); the small coupling constant observed for **36b** is representative of an axial–equatorial relationship between  $H_a$  and  $H_b$ , respectively. Based on this analysis, it was deduced that the cyclohexylidene acetal **31b** was the undesired C3-(*R*) diastereomer. Additionally, formation of the five-membered *N,O*-benzylidene acetal **37**, followed by crystallization allowed us to procure a single-crystal X-ray structure that served to establish the absolute configuration of the C3 stereocenter, the tetrasubstituted C4 (formed via the *C*-acylation), and C7 stereocenter (generated by the organocuprate or stereoconvergent cyclization reaction).<sup>37</sup>

**Generation of the C9 Stereocenter.** Having developed an efficient and stereoselective approach for the construction of the C2, C3, C4, and C7 stereocenters of kaitocephalin, formation of the remaining C9  $\alpha$ -amino acid stereocenter could now be addressed. The C9 stereocenter was envisioned to arise from the reduction of dehydroamino esters (*Z*)-**4** or (*E*)-**4** to generate an  $\alpha$ -amino ester with the desired (*S*)-stereochemistry (Scheme 1). As we could not predict a priori which olefin isomer would undergo hydrogenation to give the desired C9-(*S*)-diastereomer, we elected to perform model studies of this dehydroamino ester hydrogenation reaction on a simplified system before advancing precious kaitocephalin intermediates through the synthetic sequence.

**Model System: Synthesis of (*Z*)-Dehydroamino Ester.** The model studies on the formation and hydrogenation of pyrrolidine dehydroamino esters were initiated with the olefination of D-prolinal<sup>38</sup> using *N*-Bz-protected glycine phosphonate **38**.<sup>39,40</sup> A variety of bases were screened to examine the influence of the reaction conditions on the (*E*)-/(*Z*)-dehydroamino ester product ratio (Table 4). The use of metal hydrides (NaH) or metal amides (KHMDs) in THF resulted in the formation of mixtures of dehydroamino esters, (*Z*)-**39** and (*E*)-**39**, in ratios of 1:1–3:1, respectively (entries 1 and 2). Olefination utilizing Roush–Masamune conditions<sup>41</sup> (LiCl/DBU in  $CH_2Cl_2$ ) produced a 3:1 mixture of dehydroamino esters (*Z*)-**39** and (*E*)-**39**, respectively, in 73% combined yield (entry 3). The exclusion of LiCl, however, while retaining the use of DBU as a base,

TABLE 4. Olefination Reaction of D-Prolinal Under Various Conditions



| entry | conditions                               | yield (%) | <b>39</b> ( <i>Z</i> / <i>E</i> ) ratio <sup>a</sup> |
|-------|--|-----------|--|
| 1     | NaH, THF, –78 °C to rt                   | 50        | 1:1  |
| 2     | KHMDs/18-C-6, THF, –78 °C to rt, 16 h    | 72        | 3:1  |
| 3     | DBU, LiCl, $CH_2Cl_2$ , 0 °C to rt, 24 h | 73        | 3:1  |
| 4     | DBU, $CH_2Cl_2$ , 0 °C to rt, 24 h       | 73        | >30:1  |

<sup>a</sup> *Z/E* ratios determined by <sup>1</sup>H NMR spectroscopic analysis of crude reaction mixtures

furnished exclusively the (*Z*)-dehydroamino ester **39** with a (*Z*)/(*E*) ratio of 30:1 in 73% yield. Conditions to exclusively generate the stereochemically complementary dehydroamino ester (*E*)-**39** could not be identified. Additionally, a single-crystal X-ray structure of (*Z*)-**39** was obtained to unambiguously establish the (*Z*)-configuration.<sup>37</sup>

**Model System: Hydrogenation Studies of (*Z*)-Dehydroamino Ester.** Following the successful synthesis of the (*Z*)-dehydroamino ester (*Z*)-**39**, the key hydrogenation reaction was examined. Catalytic hydrogenation of (*Z*)-**39** over 10% Pd/C in *i*-PrOH at 15 psi of  $H_2$  furnished **40a** as a 12:1 mixture of diastereomers in 92% yield (Scheme 13).<sup>42</sup> The stereochemistry of the newly generated center of **40a** was elucidated by NOESY correlation studies performed on the derived rigid bicyclic lactam **41a** and its C2-epimer **41b** (see below).<sup>43,44</sup> In contrast to the diastereomer **41b** (see below), which displayed a positive NOE correlation between the  $\alpha$ -H and methine C–H, lactam **41a** lacked the relevant NOE correlation between the  $\alpha$ -H and methine C–H; the lack of the requisite NOE suggested that the newly generated stereocenter of **40a** was the undesired (*R*)-stereochemistry.

We next examined the hydrogenation of the dehydroamino ester (*Z*)-**39** using chiral catalysis (Table 5) in an attempt to

(36) (a) Gutowsky, H. S.; Karplus, M.; Grant, D. M. *J. Chem. Phys.* **1959**, *31*, 1278–1289. (b) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.

(37) For X-ray crystallographic data, refer to section III of the Supporting Information.

(38) Diaba, F.; Ricou, E.; Bonjoch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1437–1443.

(39) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53–60.

(40) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1993**, *58*, 4452–4461.

(41) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

(42) For other examples of highly diastereoselective substrate directed hydrogenation of dehydroamino acid derivatives, see: (a) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863–871. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555–1558. (c) Schmidt, U.; Kumpf, S.; Neumann, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1915–1916.

(43) For the use of TMSOTf in the cleavage of Boc carbamates, see: (a) Sakaitani, M.; Ohfun, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150–1158. (b) Sakaitani, M.; Ohfun, Y. *J. Org. Chem.* **1990**, *55*, 870–876. (c) Sakaitani, M.; Ohfun, Y. *Tetrahedron Lett.* **1985**, *26*, 5543–5546.

(44) . It should be noted that addition of 2 equiv of TMSOTf was crucial as the use of only 1 equiv of TMSOTf resulted in the isolation of only starting material, presumably due to initial reaction of TMSOTf with the benzamide to generate a TMS imide.



## SCHEME 13. Hydrogenation of (Z)-39 and Stereochemical Elucidation

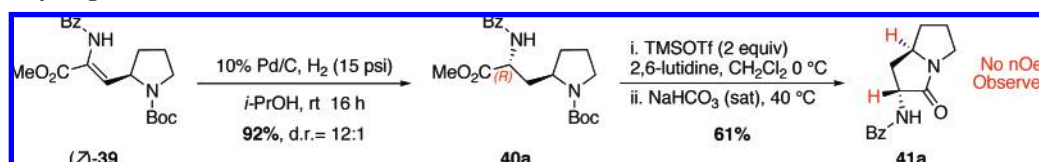


TABLE 5. Hydrogenation of (Z)-39 with Homogeneous Chiral Catalyst

| Entry | chiral catalyst                       | 40 ratio (a:b) <sup>(a)</sup> |                    |
|-------|---------------------------------------|-------------------------------|--------------------|
| 1     | [(2S,5S)-Et-DuPHOS-Rh]BF <sub>4</sub> | 1:2                           | (mis-matched case) |
| 2     | [(2R,5R)-Et-DuPHOS-Rh]BF <sub>4</sub> | 15:1                          | (matched case)     |

<sup>a</sup> Ratios determined by <sup>1</sup>H NMR spectroscopic analysis of crude reaction mixtures.

overwhelm the apparent innate preference for reduction from the “wrong” face noted for achiral catalysts. The hydrogenation of (Z)-39 using Rh-(2S,5S)-DuPHOS catalyst furnished 40b in diastereomeric ratio of 2:1 in favor of the desired (S)-stereochemistry (entry 1). The hydrogenation of (Z)-39 using Rh-(2S,5S)-DuPHOS catalyst was presumably a consequence of a mismatched stereodifferentiation, because utilizing the enantiomeric catalyst, Rh-(2R,5R)-DuPHOS, resulted in matched stereodifferentiation between the substrate and the catalyst to furnish 40a, containing the undesired (R)-stereochemistry in a 15:1 ratio (entry 2).

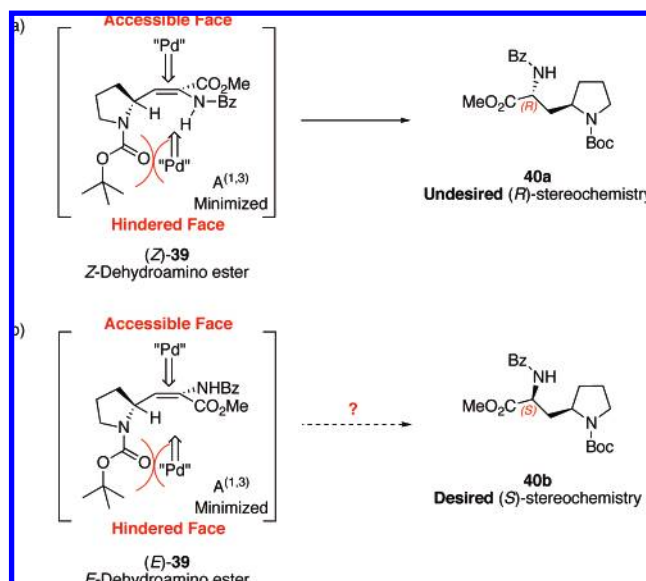


FIGURE 3. Proposed models for the reduction of (Z)-39 and (E)-39.

The predominating diastereofacial preference for the formation of the (R)-stereoisomer during the hydrogenation of (Z)-39 was rationalized by a reactive conformation that minimizes allylic (A<sup>1,3</sup>) strain in (Z)-39 (Figure 3a), resulting in the coalignment of the allylic methine (C–H) with the amine N–H.<sup>27b</sup> In addition, this model places the pyrrolidine σ<sub>C–NBoc</sub> bond parallel to the π-system of the olefin and effectively allows the Boc group to shield the *re*-face of the olefin. This conformational and stereoelectronic arrangement is mirrored in the solid state, as evidenced by the X-ray crystal structure of (Z)-39.<sup>37</sup> As a consequence, hydrogenation under heterogeneous conditions predominately delivers H<sub>2</sub> to the more accessible face of the olefin (*si*-face) via a Felkin-type transition state.

**Model System: Synthesis and Hydrogenation of Structural Congener of “(E)-Dehydroamino Ester”.** Based on the model proposed in Figure 3a, the diastereoselective formation of the requisite (S)-stereochemistry would necessitate the addition of H<sub>2</sub> to the *re*-face of the olefin (Z)-39; however, this face is hindered by the Boc group. By simple extension of this model, the hydrogenation of the corresponding *trans*-isomer (E)-39, on the now-more-accessible *re*-face, would result in the formation of the desired (S)-stereoisomer (Figure 3b). Synthetic access to (E)-39 proved to be elusive since the Horner–Wadsworth–Emmons olefination of D-prolinal failed to deliver the (E)-isomer under all conditions tested (Table 4). As a result, the alternative strategy employing a functional equivalent of (E)-39 was explored.

The key element of the ultimately successful approach circumvented the problematic olefination step by substituting (E)-39 with a synthetically accessible and chemically equivalent surrogate (Figure 4). Of particular interest in this regard was the (Z)-β-brominated dehydroamino ester ((Z)-Br-42), which is a synthetic equivalent of (E)-39 given the propensity of vinyl halides to undergo dehalogenation. We therefore selected (Z)-β-brominated dehydroamino ester ((Z)-Br-42) as a target to verify the stereochemical outcome of the hydrogenation.

The synthesis of the requisite (Z)-β-brominated dehydroamino ester ((Z)-Br-42) commenced with treatment of (Z)-39 with NBS in CH<sub>2</sub>Cl<sub>2</sub> using a protocol adapted from Coleman and co-workers (Scheme 14).<sup>40,45</sup> Subsequent addition of DABCO immediately promoted tautomerization of the α-bromo imine(s) (43) to yield mixtures of (Z)- and (E)-β-Br-dehydroamino acid isomers (Z)-Br-42 and (E)-Br-42, respectively, as judged by <sup>1</sup>H NMR spectroscopic analysis. Allowing the reaction mixture to stir over a period of 24 h at room temperature promoted the

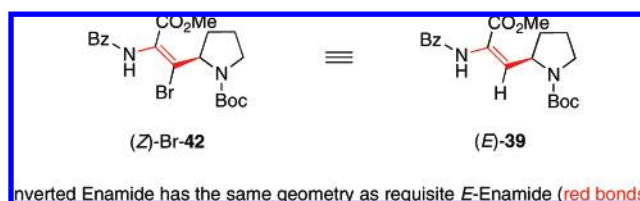
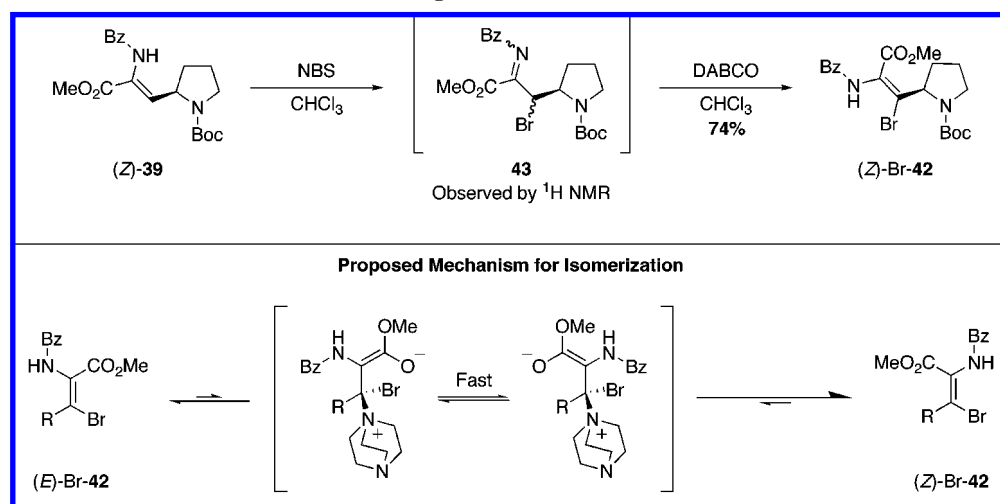
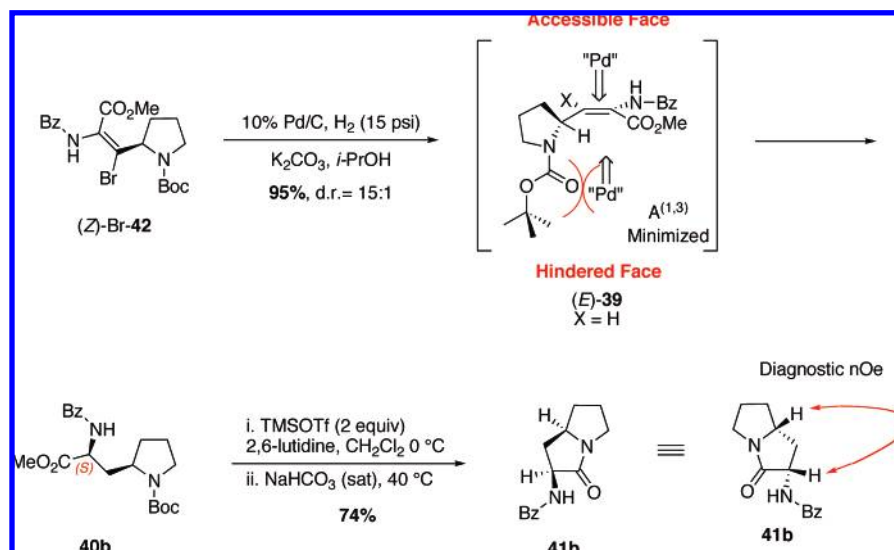


FIGURE 4. (Z)-Br-42 a structural congener of dehydroamino ester (E)-39.

SCHEME 14. Bromination/Isomerization of (Z)-42 Using NBS and DABCO



SCHEME 15. Hydrogenation of (Z)-Br-42 and Stereochemical Elucidation



complete conversion of (E)-Br-42 into the desired (Z)- $\beta$ -Br-dehydroamino ester ((Z)-Br-42), which was isolated in 74% yield as a *single* detectable isomer. The stereochemistry of the olefin was inferred on the basis of the results of the subsequent hydrogenation and bicyclic lactam formation (see Scheme 15). While the major product results from thermodynamic equilibration of the (E)-isomer, presumably via conjugate addition/elimination of the base, as shown, it is not obvious why the (Z)-isomer is the more stable of the two despite the fact that the product ratio > 10:1 clearly suggests a difference in energy of several kcal/mol favoring the (Z)-isomer (Scheme 14).

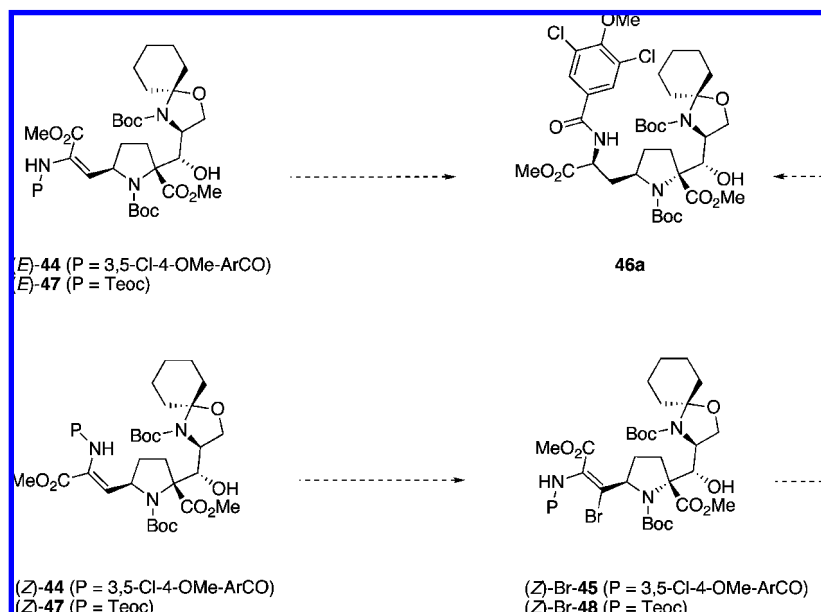
Following the successful assembly of (Z)-Br-42, the key hydrogenation was investigated (Scheme 15), which requires not only alkene hydrogenation but also stereoselective removal of the Br atom. We expected that both of these transformation of (Z)-Br-42 could be accomplished in a one-pot procedure using a heterogeneous Pd/C catalyst, since vinyl halides are readily dehalogenated with Pd/C. Treatment of (Z)-Br-42 with 10% Pd/C and  $\text{K}_2\text{CO}_3$  at 15 psi of  $\text{H}_2$  thus uneventfully furnished 40b in 95% yield as a 15:1 mixture of diastereomers, although the use of  $\text{K}_2\text{CO}_3$  as an acid (HBr) scavenger was essential to

prevent catalyst poisoning.<sup>46</sup> Careful analysis of the reaction using ESI, TLC, and reverse phase LC/MS revealed that dehalogenation of the C–Br bond is complete within 10–15 min after  $\text{H}_2$  is introduced, while hydrogenation of the olefin occurs over a period of 6 h. Furthermore, we see no indication of isomerization of the alkene bond during this process, which would result in subsequent alkene hydrogenation from the opposite face as discussed above.

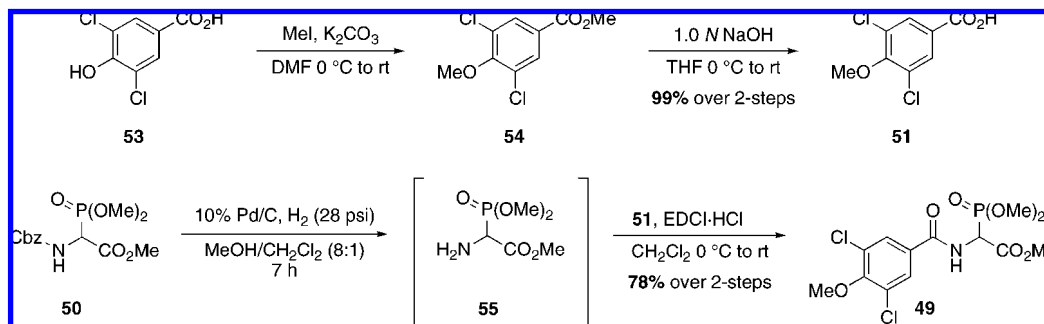
Comparison of the  $^1\text{H}$  NMR spectra in the  $\alpha\text{-H}$  region of the newly generated amino ester (4.50–4.60 ppm) of 40b (tentatively assigned as the (S)-stereochemistry) showed clear differences from that observed for 40a. To elucidate the stereochemistry of the hydrogenated product, 40b was transformed into the bicyclic lactam 41b (Scheme 15). Unlike 41a, the undesired stereoisomer, the NOESY spectrum of 41b revealed a strong NOE correlation between the  $\alpha\text{-H}$  atom and the methine

(45) For related studies on the synthesis of  $\beta$ -halogenation of dehydroamino esters, see: (a) Yamada, M.; Nakao, K.; Fukui, T.; Nunami, K. *Tetrahedron* **1996**, 52, 5751–5764. (b) Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, 59, 7635–7642. (c) Armstrong, R. W.; Tellew, J. E.; Moran, E. *J. Org. Chem.* **1992**, 57, 2208–2211.

(46) Rylander, P. N. *Catalytic Hydrogenations Over Platinum Metals*; Academic Press: New York 1967.

SCHEME 16. Proposed Conversion of (*E*)-44 and (*Z*)-44 to Amino Ester 46a

SCHEME 17. Synthesis of 3,5-Dichloro-4-methoxybenzoic Acid (51) and Phosphonate 49



C–H, providing strong evidence that the desired (*S*)-stereochemistry was produced during the dehalogenation/hydrogenation of (*Z*)-Br-42 (Scheme 15). In addition, recrystallization of bicyclic lactam **41b** from EtOAc/hexanes produced crystals that were suitable for X-ray analysis, thereby unambiguously establishing the (*S*)-configuration at the newly generated stereocenter.<sup>37</sup>

The overwhelming diastereofacial preference for the (*S*)-stereochemistry during the hydrogenation of (*Z*)-Br-42 is consistent with the hydrogenation model that was proposed (Scheme 15), in which minimization of allylic (A<sup>1,3</sup>) strain in (*Z*)-Br-42 results in the co-alignment of the allylic methine (C–H) with the ester (CO<sub>2</sub>Me).<sup>27b</sup> In addition, this model places the pyrrolidine σ<sub>C–NBoc</sub> bond parallel to the π-system of the enamide olefin and effectively allows the Boc group to shield the *si*-face of the olefin. As a consequence, the hydrogenation of (*Z*)-Br-42 under heterogeneous conditions predominately delivers H<sub>2</sub> to the most accessible *re*-face of the olefin via a Felkin-type transition state, generating the (*S*)-stereochemistry required for kaitocephalin.

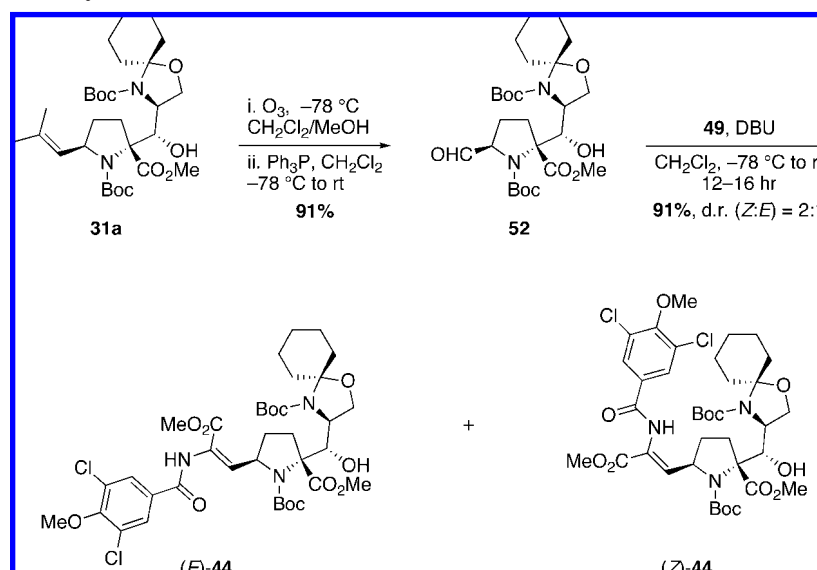
**Generation of C9-(*S*)-Stereocenter of Kaitocephalin. Formation of *N*-3,5-Dichloro-4-Methoxybenzamide Protected Dehydroamino Esters.** Guided by the outcome of the model studies, the initial approach for installing the C9-(*S*)-stereocenter of kaitocephalin required the formation of the (*E*)-dehydroamino ester ((*E*)-44)—or its synthetic equivalent the (*Z*)-Br-dehydroamino ester ((*Z*)-Br-45)—containing the appropriately pro-

TECTED 3,5-dichloro-4-hydroxy-benzamide group, followed by hydrogenation to complete the kaitocephalin carbon skeleton (Scheme 16). The key element in this strategy was to introduce simultaneously the C9-stereocenter and the 3,5-dichloro-4-hydroxybenzamide group of kaitocephalin, thereby minimizing protecting group manipulations of late stage intermediates. The main challenge in this plan is to achieve the chemo- and diastereoselective hydrogenation of the dehydroamino ester (either (*E*)-44 or (*Z*)-Br-45) without the concurrent dehalogenation of the aryl chloride groups to yield amino ester **46a**.

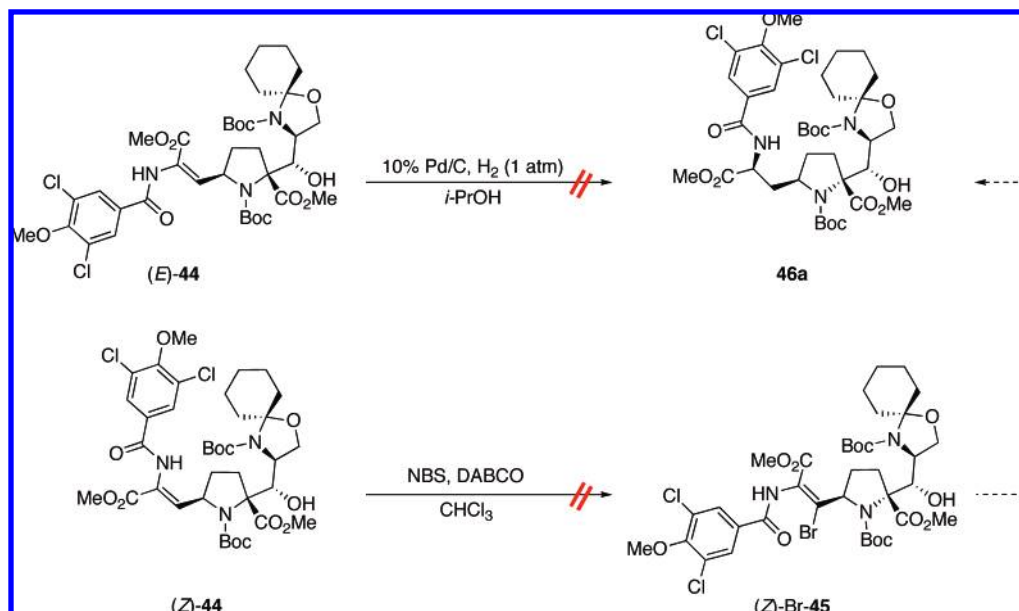
The synthesis of the dehydroamino esters commenced with the preparation of the 3,5-dichloro-4-methoxybenzamide phosphonate **49**, from phosphonate **50**<sup>39</sup> and acid **51** (Scheme 17). The olefination partner, aldehyde **52**, was prepared in >91% yield by the oxidative cleavage of alkene **31a** with ozone followed by a reductive workup (Scheme 18). Using the optimized conditions for the Horner–Wadsworth–Emmons olefination established in the prolinol model system (see entry 5, Table 4), the olefination of aldehyde **52** using phosphonate **49** in the presence of DBU furnished a 2:1 mixture of (*Z*)- and (*E*)-dehydroamino esters, (*Z*)-44 and (*E*)-44, respectively, in 91% combined yield.

The (*Z*)- and (*E*)-dehydroamino esters, (*Z*)-44 and (*E*)-44, respectively, were separable by silica gel chromatography, and each olefin isomer was carried through the reaction sequence developed in the model system: the (*E*)-dehydroamino ester ((*E*)-44) was immediately treated under hydrogenation condi-

## SCHEME 18. Synthesis of Dehydroamino Acids (Z)-44 and (E)-44



## SCHEME 19. Attempted Conversion of (Z)-44 and (E)-44 to 46a



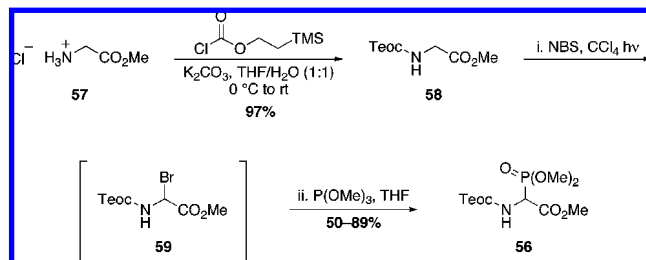
tions, while the (Z)-dehydroamino ester ((Z)-44) was to be converted into the (Z)- $\beta$ -Br-dehydroamino ester ((Z)-Br-45) prior to hydrogenation. Analogous to the model (see Scheme 16), these parallel transformations would allow the convergence of (Z)-44 and (E)-44 to a single desired product, 46a. The hydrogenation of (E)-44 using 10% Pd/C in  $i\text{-}PrOH$ , however, failed to yield any of the desired product 46a, resulting instead in considerable decomposition of the starting material (Scheme 19). Attempts to advance (Z)-44 through the bromination and isomerization reaction sequence using NBS and DABCO also met with limited success. Heating the reaction mixture in an external bath ( $65^\circ C$ ) furnished (Z)-Br-45 in only 10% yield with considerable recovery of starting material (Z)-44. The use of a more reactive brominating reagent, bromonium di-*sym*-collidine perchlorate ( $Br^+[collidine]_2ClO_4^-$ ),<sup>47</sup> only afforded an

intractable mixture that did not contain any detectable quantities of the desired product. Because of these difficulties, a slightly more circuitous route was developed to avoid subjecting the electron-deficient aryl ring to electrophilic halogenation conditions.

**Formation of N-Teoc-Protected Dehydroamino Esters.** The failure of the (Z)-dehydroamino ester bromination reaction was attributed to possible deactivation of the olefin as a result of inductive effects of the electron-withdrawing 3,5-dichloro-4-methoxyaryl amide. It was hypothesized that replacing the 3,5-dichloro-4-methoxyaryl amide with a less electron-withdrawing group might significantly improve the reactivity of the olefin toward the brominating reagent, not to mention removing the aryl ring from harm's way during the bromination step. Consequently, the amino group was protected as a trimethylsilylethoxy (Teoc) carbamate, rather than being directly acylated with the natural aryl acyl group. The general plan, outlined in Scheme 16, envisioned the formation of 46a, containing the

(47) (a) Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473–1480. (b) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190–2197.



**SCHEME 20. Synthesis of *N*-Teoc-Protected Glycine Phosphonate **56****

desired C9-(*S*)-stereochemistry, from dehydroamino esters (*E*)-**47** and (*Z*)-**47** (via (*Z*)-Br-**48**).

The formation of the requisite *N*-Teoc protected dehydroamino ester necessitated the synthesis of the *N*-Teoc protected phosphonate **56** (Scheme 20). Initial attempts to prepare **56** by hydrogenolysis of the *N*-Cbz-protected phosphonate **50** followed by treatment of the resultant amine **55** with trimethylsilylethoxy chloroformate (Teoc-Cl)<sup>48</sup> or trimethylsilylethoxy carbonylimidazole afforded **56** in low yields (5–29%). An alternative method for the construction of phosphonate **56** was devised starting from the glycine methyl ester hydrochloride salt (**57**). *N*-Acylation of **57** was accomplished by treatment with freshly prepared Teoc-Cl and K<sub>2</sub>CO<sub>3</sub> in a biphasic mixture of THF and H<sub>2</sub>O to furnish **58** in 97% yield (Scheme 20). Radical bromination of **58** employing NBS in CCl<sub>4</sub> furnished bromide **59** after 41/2 h at ambient temperature.<sup>49</sup> The unstable bromide **59** was immediately treated with P(OMe)<sub>3</sub> in THF to produce phosphonate **56** in 50–89% by an Arbuzov reaction.

Optimal conditions for the Horner–Wadsworth–Emmons olefination of aldehyde **52** and *N*-Teoc phosphonate **56** employed LDA in THF, and warming the reaction mixture from –78 °C to ambient temperatures afforded a mixture of dehydroamino esters, (*E*)-**47** and (*Z*)-**47** (dr (*E*)/(*Z*) = 1:1) respectively, in quantitative yield (Scheme 21). The (*E*)-dehydroamino ester and (*Z*)-dehydroamino ester were separable by silica gel chromatography and each isomer was characterized by diagnostic <sup>1</sup>H NMR chemical shifts and NOESY correlation studies. <sup>1</sup>H NMR spectroscopic analysis of (*Z*)-**47** revealed a downfield chemical shift for the vinyl C–H when compared to (*E*)-**47**. The downfield chemical shift of the vinyl C–H of (*Z*)-**47** is indicative of (*Z*)-olefin geometry. NOESY correlation studies disclosed characteristic NOEs between the N–H and allylic C–H for (*Z*)-**47**, whereas this NOE was absent in (*E*)-**47**.

Following the preparation of (*E*)-**47** and (*Z*)-**47**, the installation of the C9-stereocenter of kaitocephalin was addressed successfully. First, the conversion of the dehydroamino ester (*Z*)-**47** to product **46a**, containing the requisite C9-(*S*) isomer, demanded the successful bromination–isomerization, hydrogenation, Teoc removal, and finally amide bond formation. Accordingly, the (*Z*)-**47** was treated with bromonium di-*syn*-collidine hexafluorophosphorus<sup>50</sup> and Br<sup>+</sup>[collidine]<sub>2</sub>PF<sub>6</sub><sup>–</sup> to generate α-bromo imine **60**, followed by the addition of DABCO to yield the (*Z*)-Br-**48** as a 13:1 mixture of (*Z*)-/(*E*)-isomers in 86% yield (Scheme 22). Temperature control during this transformation was essential to minimize the production

of oxazolidinone side-product **61** (10%). The geometry of (*Z*)-Br-**48** was inferred based on the results obtained from the subsequent dehalogenation and hydrogenation reaction (see Scheme 23).

Subsequent dehalogenation and hydrogenation of (*Z*)-Br-**48** was accomplished using 20 mol % of 10% Pd/C and K<sub>2</sub>CO<sub>3</sub> in *i*-PrOH under 15 psi of H<sub>2</sub> to afford **62a** as a >13:1 mixture of C9 diastereomers in 98% yield (Scheme 23a). Careful monitoring of the reaction by ESI-MS and TLC provided evidence for the dehalogenation of the vinyl-Br (C–Br → C–H) within 10–15 min, followed by slow hydrogenation of the olefin to yield **62a**. The catalytic hydrogenation of the dehydroamino ester (*E*)-**47** using 20 mol % of 10% Pd/C in *i*-PrOH at one atmosphere of H<sub>2</sub> afforded **62a** in 95% yield as a *single* diastereomer (Scheme 23), thereby successfully converging both dehydroamino esters to the desired intermediate. The diastereoselectivity observed for the hydrogenation of (*Z*)-Br-**48** and (*E*)-**47** can be rationalized via a model analogous to that proposed for the diastereofacial hydrogenation of the proline model system (see Figure 3).

The initial experiments for the installation of the C9-stereocenter of kaitocephalin were performed on separated samples of (*E*)-**47** and (*Z*)-**47**. For practical reasons, however, we sought to minimize the separate processing of isolated samples of (*E*)-**47** and (*Z*)-**47** through the reaction sequence. Ultimately, it was determined that the diastereomeric mixture of (*E*)-**47** and (*Z*)-**47** produced from the Horner–Wadsworth–Emmons olefination reaction could be directly and efficiently converted into pure (*Z*)-Br-**48** (Scheme 24) without separation. To that end, a 1:1 diastereomeric mixture of (*E*)-**47** and (*Z*)-**47**, obtained from the olefination of aldehyde **52**, was subjected to Br<sup>+</sup>[collidine]<sub>2</sub>PF<sub>6</sub><sup>–</sup>, followed by the addition of DABCO to provide the (*Z*)-Br-**48** in 90% yield as a chromatographically inseparable >13:1 mixture of (*Z*)-Br and (*E*)-Br isomers.<sup>51</sup> Catalytic hydrogenation of (*Z*)-Br-**48** over Pd/C in the presence of K<sub>2</sub>CO<sub>3</sub> furnished **62a** as a single detectable diastereomer in 98% yield.

**End Game: Completion of the Synthesis of Kaitocephalin**

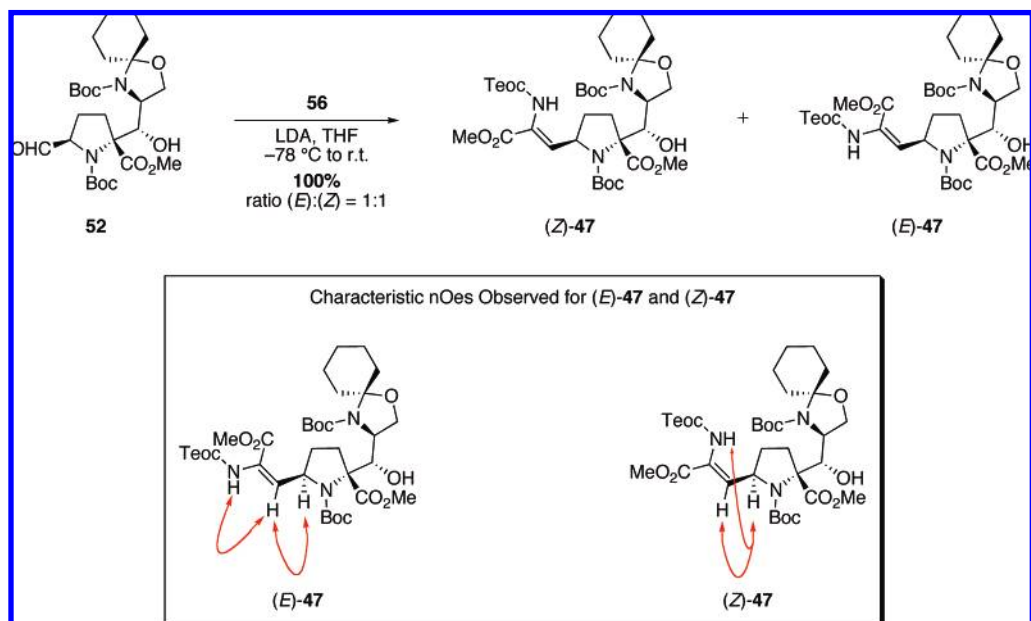
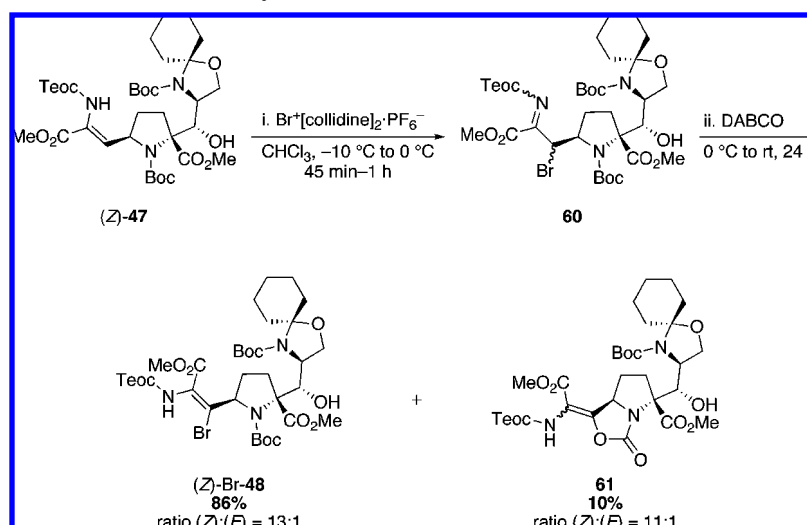
Following the successful preparation of **62a**, which contains the complete carbon backbone and all of stereogenic centers of the natural product, we were poised to complete the total synthesis of **1**. At that point, all that remained was the introduction of the 3,5-dichloro-4-hydroxyaryl amide, formation of the C1 carboxylic acid, and removal of the protecting groups. Introduction of the 4-methoxy-3,5-dichloroaryl amide necessitated the removal of the Teoc protecting group, which proved to be a delicate task. Exposure of **62a** to commercially available TBAF (1.0 M in THF) or solid TBAF·3H<sub>2</sub>O cleanly removed the Teoc carbamate; the resultant amino ester, however, was generated with varying degrees of epimerization at the C9 center, which presumably occurred as a consequence of the basic reaction conditions. In an attempt to attenuate the basicity of the F<sup>–</sup> anion in the reaction mixture, the TBAF deprotection of **62a** was buffered with AcOH, which unfortunately suppressed the deprotection process completely.

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(51) The (*E*)-dehydroamino ester ((*E*)-**47**) reacted with Br<sup>+</sup>[collidine]<sub>2</sub>PF<sub>6</sub><sup>–</sup> within 5–6 min to yield the α-Br imine, while the conversion of the (*Z*)-dehydroamino ester ((*Z*)-**47**) to the corresponding α-Br imine occurred over 60–90 min.

SCHEME 21. Olefination of **52** with *N*-Teoc Phosphonate **56**SCHEME 22. Bromination/Isomerization of Dehydroamino Ester (*Z*)-**47**

We then conjectured that sparingly soluble sources of  $\text{F}^-$  anion,<sup>52</sup> such as  $\text{CsF}^{53}$  or  $\text{KF}^{54}$  might sufficiently attenuate the basicity of the reaction mixture to allow for deprotection of the Teoc group without compromising the stereochemical integrity of the C9-stereocenter. Gratifyingly, addition of a solution of **62a** in DMSO to freshly dried  $\text{CsF}$  cleanly deprotected the Teoc carbamate after 13 h to afford amino ester **63** in near quantitative yield, with no detectable epimerization at the C9-stereocenter (Scheme 25). Subsequent amide coupling with 4-methoxy-3,5-dichlorobenzoic acid **51** was effected with the aid of  $\text{EDCI}\cdot\text{HCl}$  to yield **46a** in 94% yield over two steps.

Completion of the synthesis proceeded uneventfully with the hydrolysis of the cyclohexylidene *N,O*-acetal **46a**, which was accomplished using aqueous 80%  $\text{AcOH}$  at ambient temperatures to furnish amino diol **64** (Scheme 25). Chemoselective

oxidation of diol **64** was then achieved with catalytic TEMPO and  $\text{NaOCl}_2$  to provide carboxylic acid **65** in 88% yield from acetal **46a**.<sup>55</sup> The susceptibility of the C2–N in **65** toward lactam formation (with the C18 ester) precluded the use of harsh Lewis acids, mineral acids, or strong base for the deprotection of the methyl ether and methyl esters. Ultimately, it was determined that treatment of **65** with  $\text{LiI}$  in  $\text{EtOAc}$  ( $60\text{--}80\text{ }^{\circ}\text{C}$ ) over a period of 1 week effectively promoted the cleavage of the methyl ether and esters,<sup>56</sup> which was followed by the in situ deprotection of the Boc carbamates using trifluoroacetic acid (TFA) to deliver crude kaitocephalin (**1**) as a dark brown solid.

Purification of the crude product by reversed-phase HPLC under acidic conditions (10:90  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  with 0.1% TFA) followed by lyophilization afforded kaitocephalin (**1**) as the *bis*-

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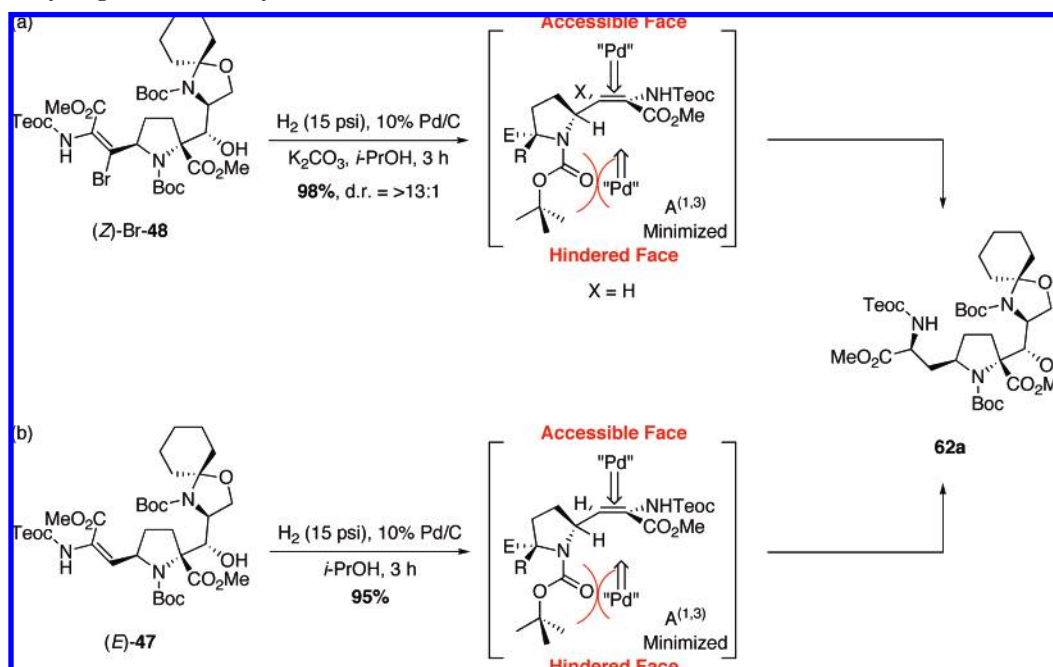
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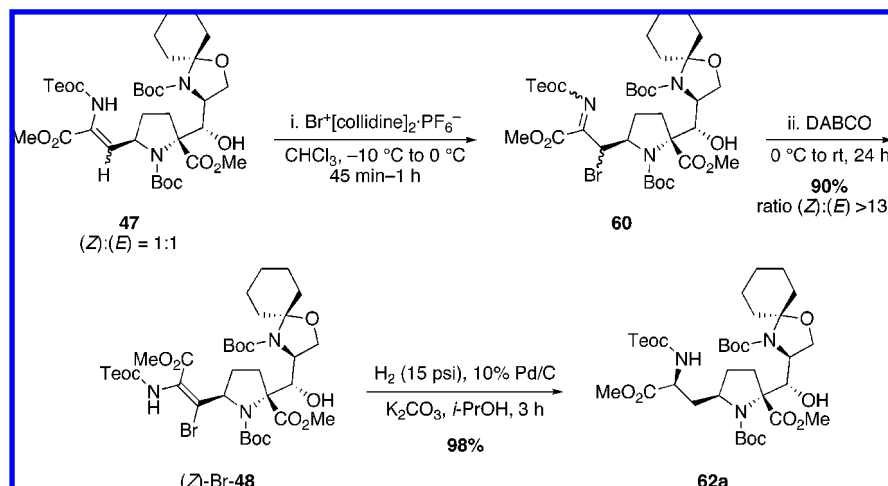
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SCHEME 23. Hydrogenation of Dehydroamino Esters (Z)-Br-48 and (E)-47



SCHEME 24. Efficient Conversion of Mixtures of (E)-47 and (Z)-47 to 62a



TFA salt in 20% yield (>72% yield per protecting group removed, five in all). The lactam **67** was also isolated during HPLC purification, which presumably arises as a result of acid (TFA)-catalyzed cyclization of the C2 amine onto the C18 ester. High-resolution mass spectrometry analysis of purified **1** correlated with the reported mass of kaitocephalin, and <sup>1</sup>H NMR, <sup>13</sup>C NMR, and optical rotation [observed [α]<sub>D</sub><sup>25</sup> -35.4 (c 0.13, H<sub>2</sub>O) [lit.<sup>5a</sup> [α]<sub>D</sub><sup>21</sup> -31.0 (c 0.70, H<sub>2</sub>O), lit.<sup>7a</sup> [α]<sub>D</sub><sup>25</sup> -26.6 (c 0.19, H<sub>2</sub>O), lit.<sup>8</sup> [α]<sub>D</sub><sup>24</sup> -29.0 (c 0.30, H<sub>2</sub>O)]] were consistent with the natural compound, although the <sup>1</sup>H NMR coincided perfectly with the published spectrum of kaitocephalin only after conversion of the bis-TFA salt of **1** to its mono-diethylammonium salt with a 2 mM aqueous solution of pH 7.0 Et<sub>2</sub>NH/CO<sub>2</sub> buffer.<sup>57,58</sup>

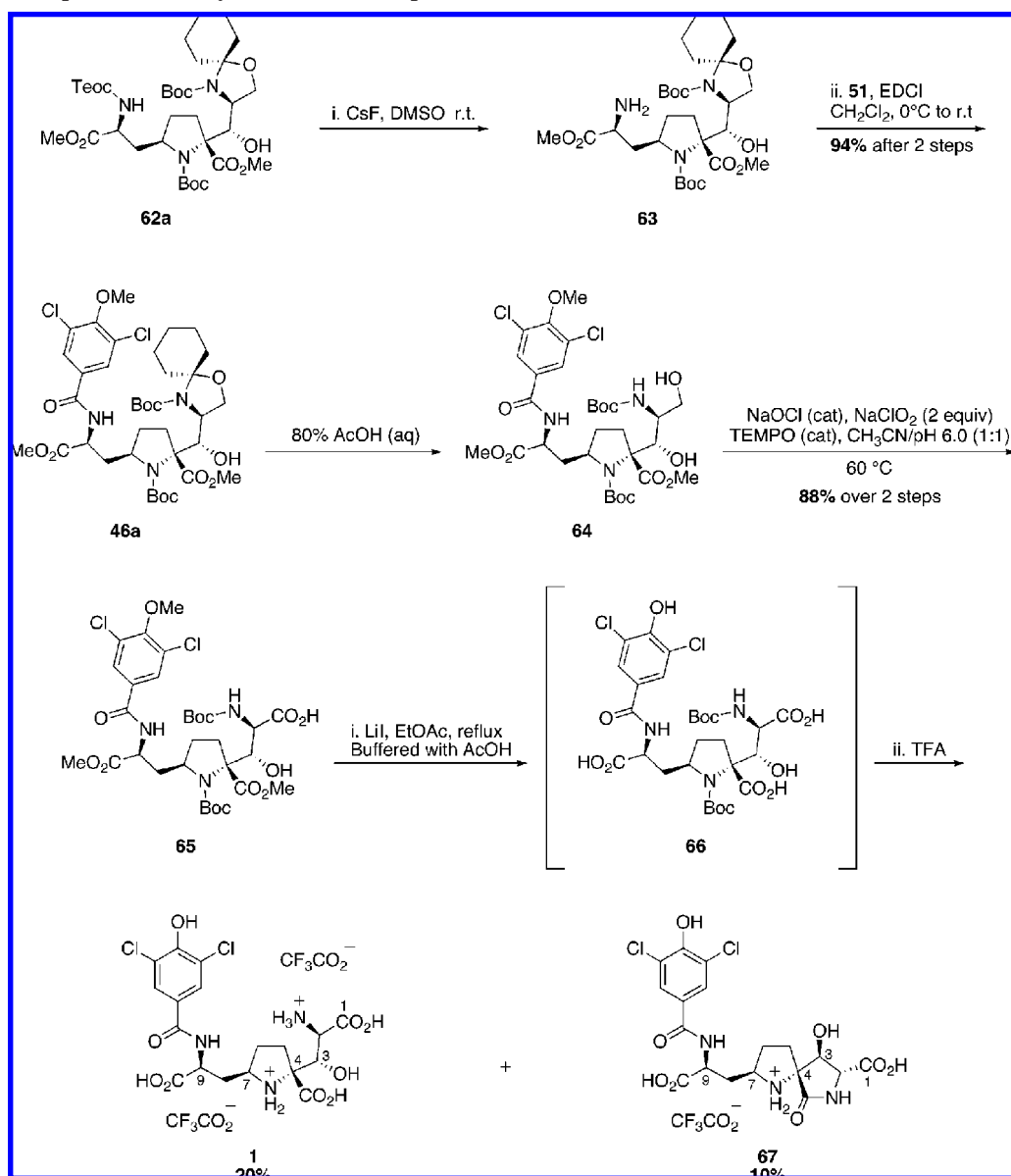
(57) The published proton NMR spectrum for the kaitocephalin clearly shows signals assignable to the diethylammonium counterion; however, they were not included in the tabulated <sup>1</sup>H NMR data included in the Experimental Section.

## Conclusion

The studies reported in this paper culminated in the total synthesis of (-)-kaitocephalin in 11 steps (eight isolated and purified intermediates) and 6% overall yield starting from the known intermediate *trans*-**6**. The overall efficiency profited from the use of substrate-controlled manipulations to establish the requisite C3, C4, C7, and C9 stereocenters. Two strategies were developed for the diastereoselective formation of the *trans*-2,5-disubstituted pyrrolidine core (*trans*-**6**) of kaitocephalin containing the C7 stereocenter. The first approach utilized a standard diastereoselective organocuprate addition to a chiral *N*-acyliminium ion; the second and ultimately superior strategy employed a novel stereoconvergent cyclization reaction for the preparation of the *trans*-2,5-disubstituted pyrrolidine core. The C4 and C3

(58) We thank Dr. Shin-ya for sending a sample of kaitocephalin that we requested for HPLC comparison; unfortunately, HPLC and HRMS analysis of the material that was received revealed only decomposition products.

## SCHEME 25. Completion of the Synthesis of Kaitocephalin



stereocenters of kaitocephalin were introduced sequentially using a diastereoselective modified Claisen condensation and a chemo- and diastereoselective DIBALH reduction of the  $\beta$ -keto ester **30**. The stereochemistry of the C9-(*S*)-amino ester was established with excellent control by the substrate directed hydrogenation of a dehydroamino ester derivative to complete the carbon skeleton of kaitocephalin and introduce the C9-(*S*) stereocenter as a *single* diastereomer. This route allows for the preparation of several key intermediates in gram-scale quantities, which in turn provides relatively large quantities of kaitocephalin for complete biological evaluation.

## Experimental Section

**$\beta$ -Keto Ester 30.** Under a constant atmosphere of N<sub>2</sub>, ester *trans*-**6** (4.70 g, 16.6 mmol) was diluted with THF (31.0 mL) and cooled to –78 °C. Freshly prepared LDA (24.0 mL, 24.0 mmol, 1.00 M in THF) was added dropwise over 10 min. The reaction mixture was allowed to stir for 3 h at –78 °C, after which time a solution of **26** (8.44 g, 25.2 mmol) in THF (20.0 mL) was added dropwise over 15 min. After 90 min at –78 °C, the reaction was

quenched by the addition of AcOH in THF (50.0 mL, 10% AcOH in THF). The mixture was placed in a 0 °C bath and allowed to stir for 15 min, and then saturated NaHCO<sub>3</sub> (50.0 mL) was added. After 20 h, the blue reaction mixture was extracted, diluted with H<sub>2</sub>O (50.0 mL), and extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with 1.0 N NaHSO<sub>4</sub> (100 mL) and brine (500 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo to afford a green foam. <sup>1</sup>H NMR analysis of unpurified material revealed that  $\beta$ -keto ester **30** was formed as a *single* diastereomer. The foam was purified by flash chromatography (gradient elution 5:95–10:90–20:80–100:0 EtOAc/hexanes) to yield  $\beta$ -keto ester **30** as a white foam (4.46 g, 49%, *single* diastereomer): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>, 375 K)  $\delta$  5.35 (app dsep, *J* = 8.9, 1.3, 1H), 4.92–4.90 (m, 1H), 4.63 (td, *J* = 8.8, 1.8, 1H), 4.01–3.98 (m, 2H), 3.71 (s, 3H), 2.55 (ddd, *J* = 12.2, 6.1, 2.7, 1H), 2.30–2.08 (td, *J* = 12.0, 6.5, 1H and m, 3H), 1.86–1.82 (m, 1H), 1.72 (d, *J* = 1.1, 3H), 1.67 (d, *J* = 1.2, 3H), 1.62–1.54 (m, 4H), 1.54–1.50 (m, 1H), 1.50–1.45 (m, 2H), 1.42 (s, 9H), 1.38 (s, 9H), 1.18–1.07 (m, 1H); <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, only major rotamer reported at 298 K)  $\delta$  204.6, 170.8, 154.8, 151.8, 131.5, 126.4, 95.7, 80.4, 80.3, 77.3, 66.3, 60.7, 57.9, 52.9, 35.7,



33.4, 33.2, 31.5, 28.5, 28.3, 25.7, 25.2, 23.7, 23.5, 18.1; IR (KBr) 2976, 2933, 2868, 1754, 1720, 1694, 1454, 1392, 1366, 1257, 1159  $\text{cm}^{-1}$ ; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{46}\text{N}_2\text{O}_8$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 573.3152, found 573.3137;  $[\alpha]_D^{25} +66.6$  ( $c$  0.64,  $\text{CHCl}_3$ ).

**$\beta$ -Hydroxy Ester 31a.** Under a constant atmosphere of Ar,  $\beta$ -keto ester **30** (3.98 g, 7.23 mmol) was diluted with THF (102 mL) and cooled to  $-78^\circ\text{C}$ . To this cooled solution was added DIBALH (1.0 M in toluene, 10.0 mL, 10.0 mmol, 1.38 equiv). The reaction mixture was allowed to warm to ambient temperature overnight. The reaction was cooled ( $0^\circ\text{C}$ ) and quenched with saturated aqueous sodium–potassium tartrate (10 mL). The resultant biphasic suspension was warmed to room temperature and stirred vigorously for 30 min, and aqueous 1.0 N  $\text{NaHSO}_4$  (30 mL) was added to remove emulsions. The organic phase was separated, and the aqueous phase was extracted with EtOAc ( $4 \times 50$  mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , and concentrated in vacuo to provide a pink foam. Normal-phase HPLC analysis (2:98 *i*-PrOH/hexanes, 1.0 mL/min, 220 nm) of the unpurified material revealed dr (**31a/31b**) = 30.0:1.00. The foam was purified by flash chromatography (gradient elution 10:90–40:60 EtOAc/hexanes) to yield  $\beta$ -hydroxy ester **31a** as a white foam (3.45 g, 86%, dr **31a/31b** = > 30:1). **31a:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 375 K)  $\delta$  5.32 (app dsep,  $J = 8.9$ , 1.4, 1H), 5.25 (br s, 1H), 4.57 (td,  $J = 8.4$ , 3.3, 1H), 4.43 (br s, 1H), 4.05 (ddd,  $J = 6.9$ , 3.5, 1.8, 1H), 4.01 (dd,  $J = 8.8$ , 3.5, 1H), 3.84 (dd,  $J = 8.8$ , 6.9, 1H), 3.70 (s, 3H), 2.41–2.36 (m, 1H), 2.25–2.05 (m, 4H), 1.81–1.78 (m, 1H), 1.69 (d,  $J = 1.3$ , 3H), 1.63 (d,  $J = 1.2$ , 3H), 1.61–1.55 (m, 3H), 1.53–1.47 (m, 4H and s, 9H), 1.40 (s, 9H), 1.15–1.07 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , only major rotamer reported at 298 K)  $\delta$  173.2, 157.2, 152.8, 131.1, 126.1, 94.6, 81.1, 80.1, 75.3, 73.9, 62.2, 59.9, 58.1, 52.8, 34.5, 34.4, 32.7, 30.9, 28.6, 28.4, 25.6, 25.2, 23.7, 23.5, 17.9; IR (KBr), 3358, 2977, 2932, 2863, 1750, 1693, 1455, 1392, 1366, 1253, 1160  $\text{cm}^{-1}$ ; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}_8$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 575.3308, found 575.3300;  $[\alpha]_D^{25} -60.1$  ( $c$  0.78,  $\text{CHCl}_3$ ).

**31b:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 375 K)  $\delta$  5.46 (app dsep,  $J = 8.8$ , 1.3, 1H), 4.56 (td,  $J = 8.5$ , 3.1, 1H), 4.31 (dd,  $J = 9.0$ , 5.5, 1H), 4.07 (d,  $J = 5.3$ , 1H), 4.00 (dd,  $J = 9.0$ , 4.8, 1H), 3.77 (dd,  $J = 8.7$ , 5.0, 1H), 3.68 (s, 3H), 3.63 (d,  $J = 8.7$ , 1H), 2.69 (ddd,  $J = 13.2$ , 8.7, 4.2, 1H), 2.32–2.18 (m, 3H), 2.04 (ddd,  $J = 13.5$ , 9.2, 9.2, 1H), 1.70 (d,  $J = 0.92$ , 3H), 1.64 (d,  $J = 1.1$ , 3H), 1.63–1.56 (m, 3H), 1.54–1.47 (m, 4H), 1.44 (s, 9H), 1.36 (s, 9H), 1.17–1.10 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , only major rotamer reported at 298 K)  $\delta$  175.8, 154.8, 152.3, 132.2, 127.3, 94.6, 81.2, 80.0, 74.0, 72.1, 66.4, 59.3, 57.5, 52.5, 36.1, 35.6, 32.3, 31.2, 28.5, 28.3, 28.2, 25.9, 25.0, 23.3, 17.9; IR (KBr), 3358, 2977, 2932, 2863, 1750, 1693, 1455, 1392, 1366, 1253, 1160  $\text{cm}^{-1}$ ; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{48}\text{N}_2\text{O}_8$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 575.3308, found 575.3305;  $[\alpha]_D^{25} +12.7$  ( $c$  0.27,  $\text{CHCl}_3$ ).

**33:** isolated as a white solid (0.302 g, 7.9%);  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ , 375 K)  $\delta$  5.28 (app dsep,  $J = 8.7$ , 1.4, 1H), 4.75 (br s, 1H), 4.58 (td,  $J = 8.2$ , 3.1, 1H), 4.28 (s, 1H), 4.06 (ddd,  $J = 7.1$ , 3.8, 1.3, 1H), 3.99 (dd,  $J = 8.6$ , 3.7, 1H), 3.85–3.82 (dd,  $J = 8.6$ , 7.2, 1H and d,  $J = 11.1$ , 1H), 3.75 (d,  $J = 10.8$ , 1H), 2.26–2.21 (m, 1H), 2.11–2.01 (m, 3H), 1.95–1.91 (m, 1H), 1.84–1.80 (m, 1H), 1.66 (d,  $J = 1.2$ , 3H), 1.62 (d,  $J = 1.1$ , 3H), 1.61–1.55 (m, 4H), 1.53–1.46 (m, 3H and s, 9H), 1.43–1.40 (m, 1H), 1.38 (s, 9H), 1.14–1.07 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , only major rotamer reported at 298 K)  $\delta$  156.6, 153.0, 130.8, 127.7, 94.6, 81.2, 80.5, 74.7, 70.5, 65.8, 65.1, 62.7, 59.4, 58.6, 35.7, 31.6, 30.2, 28.5, 28.4, 25.6, 25.0, 23.5, 23.3, 18.0; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}_7$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 547.3359, found 547.3344.

**$\beta$ -Bromo Enamide 48.** To a cooled ( $0^\circ\text{C}$ ) solution of (*E*)-**47** and (*Z*)-**47** (2.00 g, 2.70 mmol, 1:1 mixture of (*E*)-**47**:(*Z*)-**47**) in  $\text{CHCl}_3$  (35 mL) was added  $\text{Br}[\text{collidine}]_2\text{PF}_6$  (1.51 g, 3.23 mmol). The resultant suspension was stirred vigorously at  $0^\circ\text{C}$ . The progress of the reaction was monitored by TLC (30:70 EtOAc/hexanes). After 5 min, complete consumption of (*E*)-**47** was observed by TLC analysis, and after 1 h the disappearance of (*Z*)-

**47** was detected. Solid DABCO (1.50 g, 13.4 mmol) was added in one portion, and the reaction mixture was allowed to gradually warm to room temperature over 3 h. After being stirred for an additional 16 h, the yellow suspension was concentrated in vacuo, diluted with EtOAc (100 mL), and washed with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  ( $2 \times 50$  mL). The aqueous layer was extracted with EtOAc ( $3 \times 100$  mL). The combined organic extracts were washed with 1.0 N  $\text{NaHSO}_4$  (aq) ( $3 \times 50$  mL), saturated  $\text{NaHCO}_3$  (100 mL), and brine (100 mL). The organic extract was dried over  $\text{MgSO}_4$  and concentrated to give a white foam. Normal-phase HPLC analysis (2:98 *i*-PrOH/hexanes, 1.0 mL/min, 254 nm) of the unpurified material revealed a ratio of (*Z*)-**Br-48**:(*E*)-**Br-48** = 13.3:1.00. The foam was purified by flash chromatography (gradient elution 20:80–60:40 EtOAc/hexanes) to yield an inseparable mixture of (*Z*)-**Br-48**:(*E*)-**Br-48** as a white foam (2.00 g, 90%, dr (*Z*)-**Br-48**:(*E*)-**Br-48** = 13.0:1.0).

**(Z)-Br-48:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 385 K)  $\delta$  8.16 (br s, 1H), 5.08 (app t,  $J = 7.5$ , 1H), 4.71 (d,  $J = 2.9$ , 1H), 4.16–4.12 (m, 3H), 4.07 (ddd,  $J = 6.4$ , 3.2, 3.2, 1H), 3.79 (dd,  $J = 8.8$ , 6.6, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 2.35 (ddd,  $J = 12.8$ , 7.9, 4.9, 1H), 2.26–2.15 (m, 3H), 2.09 (td,  $J = 13.3$ , 4.3, 1H), 1.82–1.80 (m, 1H), 1.78–1.71 (m, 1H), 1.61–1.58 (m, 3H), 1.54–1.50 (m, 3H), 1.46 (s, 9H), 1.39 (s, 9H), 1.16–1.08 (m, 1H), 0.99–0.96 (m, 2H), 0.06 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , only major rotamer reported at 298 K)  $\delta$  171.5, 163.0, 155.4, 153.5, 152.8, 127.3, 126.5, 94.8, 82.1, 80.3, 75.5, 75.0, 64.8, 62.7, 62.1, 57.8, 52.9, 52.5, 35.0, 32.1, 29.6, 28.6, 28.6, 28.3, 25.1, 23.6, 23.5, 17.7,  $-1.5$ ; IR (thin film) 3414, 3319, 3006, 2952, 2865, 1732, 1693, 1632, 1479, 1393, 1367, 1320, 1250, 1172  $\text{cm}^{-1}$ ; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{35}\text{H}_{58}\text{BrN}_3\text{O}_{12}\text{Si}$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 842.2871, found 842.2856;  $[\alpha]_D^{25} +5.2$  ( $c$  0.20,  $\text{CHCl}_3$ ).

**Amino Ester 62a.** Under a constant atmosphere of  $\text{N}_2$  (g), 10% Pd/C (0.344 g, 0.325 mmol, 20 mol %) was added to a suspension of (*Z*)-**Br-48** (1.34 g, 1.63 mmol, dr (*Z*)-**Br-48**:(*E*)-**Br-48** = 13.0:1.0) and  $\text{K}_2\text{CO}_3$  (0.378 g, 2.73 mmol) in *i*-PrOH (67 mL). Three cycles of evacuation (30 s) followed by purging with  $\text{N}_2$  (g) was conducted. To the partially degassed suspension was introduced  $\text{H}_2$  (g) (1 atm) via a  $\text{H}_2$  (g) filled balloon, followed by three cycles of evacuation (30 s) and purging with  $\text{H}_2$  (g). After 6 h, excess  $\text{H}_2$  (g) was removed by three cycles of evacuation (30 s) and purging with  $\text{N}_2$  (g). The suspension was filtered over a pad of Celite (1.5 in. thick), the pad was washed with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL), and the filtrate was concentrated in vacuo to give a white foam.  $^1\text{H}$  NMR analysis of the unpurified material revealed one major diastereomer, dr (**62a/62b**) = >13.2:1.0. The foam was purified by flash chromatography (gradient elution 10:90–20:80–40:60 EtOAc/hexanes) yielded **62a** as a white foam (1.18 g, 98%).

**62a:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 375 K)  $\delta$  6.94 (d,  $J = 7.5$ , 1H), 5.26 (br s, 1H), 4.43 (dd,  $J = 9.5$ , 1.4, 1H), 4.12–4.08 (m, 3H), 4.02–4.00 (m, 1H), 3.97 (dd,  $J = 8.9$ , 3.4, 1H), 3.94–3.91 (m, 1H), 3.82 (dd,  $J = 8.9$ , 7.0, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 2.42–2.37 (app m, 1H), 2.29 (ddd,  $J = 14.0$ , 5.9, 2.2, 1H), 2.24–2.18 (m, 2H), 2.08 (td,  $J = 13.4$ , 4.3, 1H), 2.00–1.92 (m, 1H), 1.81–1.76 (m, 2H), 1.67 (ddd,  $J = 14.0$ , 9.9, 8.1, 1H), 1.62–1.56 (m, 3H), 1.52–1.49 (m, 3H and s, 9H), 1.47–1.42 (s, 9H), 1.15–1.06 (m, 1H), 0.97–0.93 (m, 2H), 0.05 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , only major rotamer reported at 298 K)  $\delta$  173.1, 172.6, 156.5, 156.2, 152.8, 94.6, 82.3, 80.2, 75.4, 73.4, 63.7, 61.8, 59.6, 57.9, 52.9, 52.8, 52.5, 36.1, 34.4, 33.8, 32.5, 28.8, 28.5, 28.4, 25.1, 23.6, 23.5, 17.7,  $-1.46$ ; IR (thin film) 3332, 2953, 2943, 2863, 1749, 1720, 1696, 1681, 1390, 1367, 1250, 1161  $\text{cm}^{-1}$ ; HRMS (ESI/methanol)  $m/z$  calcd for  $\text{C}_{35}\text{H}_{61}\text{N}_3\text{O}_{12}\text{Si}$  ( $\text{M} + \text{Na}$ )<sup>+</sup> 766.3922, found 766.3942;  $[\alpha]_D^{25} -21.1$  ( $c$  0.60,  $\text{CHCl}_3$ ).

**62b:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 375 K)  $\delta$  6.64 (d,  $J = 7.6$ , 1H), 4.44 (d,  $J = 7.6$ , 1H), 4.12–4.02 (m, 4H), 3.99–3.95 (m, 2H), 3.83 (dd,  $J = 8.8$ , 7.0, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.43–2.39 (m, 1H), 2.24–2.17 (m, 2H), 2.15–2.05 (m, 2H), 2.02–1.94 (m, 1H), 1.82–1.77 (m, 2H), 1.70–1.65 (m, 1H), 1.61–1.55 (m, 3H), 1.54–1.49 (m, 2H), 1.47 (s, 9H), 1.47–1.44 (s, 9H and m,

1H), 1.16–1.07 (m, 1H), 0.97–0.94 (m, 2H), 0.05 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, only major rotamer reported at 298 K) δ 173.1, 172.6, 156.6, 156.4, 152.8, 94.6, 82.3, 80.2, 75.4, 73.6, 63.7, 61.8, 58.6, 57.9, 53.0, 52.7, 52.0, 35.8, 34.4, 33.8, 32.6, 28.7, 28.6, 27.8, 25.1, 23.6, 23.4, 17.7, –1.44; IR (thin film) 3332, 2954, 2933, 2863, 1747, 1720, 1696, 1679, 1390, 1368, 1250, 1161 cm<sup>–1</sup>; HRMS (ESI/methanol) *m/z* calcd for C<sub>35</sub>H<sub>61</sub>N<sub>3</sub>O<sub>12</sub>Si (M + Na)<sup>+</sup> 766.3922, found 766.3920; [α]<sub>D</sub><sup>25</sup> –18.4 (*c* 0.17, CHCl<sub>3</sub>).

**Bis-TFA Salt 1.** To a mixture of **65** (0.144 g, 0.195 mmol) in anhydrous EtOAc (5 mL) was added LiI (0.276 g, 2.07 mmol) in one portion. The resulting brown homogeneous reaction mixture was heated (60 °C) in an oil bath. After 30 h, the formation of solid precipitates was observed, and AcOH (0.10 mL) was added to solubilize the precipitates. The consumption of starting material **65** was monitored by LC/MS (C18-reversed-phase HPLC, gradient elution 2:98–95:5 CH<sub>3</sub>CN/H<sub>2</sub>O with 0.1% AcOH). Over the course of 5 days, additional LiI (0.342 g, 2.56 mmol) and AcOH (0.50 mL) were introduced to the reaction mixture, and the external bath temperature was increased (90 °C). After complete consumption of **65** was judged by LC/MS analysis, the reaction was allowed to cool to room temperature, concentrated in vacuo, and dried (0.50 mmHg) to afford a brown paste.

To a cooled (0 °C) solution of the resultant brown paste in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added TFA (10.0 mL, 130 mmol). After 1 h, the reaction was concentrated in vacuo, and excess TFA was azeotropically removed by co-distillation with hexanes (5 × 25 mL) to afford a brown solid. The solid was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (30 mL). The aqueous phase was separated, and the brown organic phase was washed with H<sub>2</sub>O (3 × 25 mL) and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL). The combined aqueous phases were lyophilized to afford an off-white solid. The resultant solid was purified by preparatory reversed-phase HPLC (10:90 CH<sub>3</sub>CN:H<sub>2</sub>O with 0.8% TFA, 210 nm), and the collected fractions were lyophilized to furnish the bis-TFA salt of **1** as a white powder (0.028 g, 20%) and the TFA salt of **67** as a white powder (0.011 g, 9.6%).

**Bis-TFA salt 1:** <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 7.81 (s, 2H), 4.60 (dd, *J* = 8.4, 5.5, 1H), 4.54 (s, 1H), 4.30 (s, 1H), 3.89–3.82 (m, 1H), 2.59 (ddd, *J* = 13.8, 6.8, 6.8, 1H), 2.42 (ddd, *J* = 13.5, 6.4, 2.4, 1H), 2.28–2.20 (m, 2H), 2.15 (ddd, *J* = 13.5, 11.2, 6.7, 1H), 1.78–1.70 (m, 1H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O, uncalibrated)<sup>59</sup> δ 174.2, 170.6, 167.8, 151.5, 128.0, 125.9, 122.0, 76.6, 70.5, 58.6, 55.6, 52.4, 34.1, 31.9, 29.7; HRMS (ESI/methanol) *m/z* calcd for C<sub>18</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>9</sub> (M + Na)<sup>+</sup> 516.0552, found 516.0557; [α]<sub>D</sub><sup>25</sup> –35.4 (*c* 0.13, H<sub>2</sub>O).

**TFA salt 67:** <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 7.88 (s, 2H), 4.60 (d, *J* = 7.4, 1H), 4.53 (dd, *J* = 9.1, 5.0, 1H), 3.94–3.89 (d, *J* = 7.4, 1H and m, 1H), 2.63–2.57 (m, 2H), 2.39–2.33 (m, 1H), 2.27 (ddd, *J* = 14.8, 8.9, 6.2, 1H), 2.13 (ddd, *J* = 13.7, 8.3, 3.3, 1H), 2.04–1.96 (m, 1H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O, uncalibrated)<sup>59</sup> δ 175.7, 174.9, 171.8, 167.7, 151.5, 127.9, 125.8, 122.0, 73.8, 72.5, 61.1, 59.9, 52.6, 34.0, 29.4, 27.2; HRMS (ESI/methanol) *m/z* calcd for C<sub>18</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>8</sub> (M + H)<sup>+</sup> 476.0627, found 476.0613; [α]<sub>D</sub><sup>25</sup> –7.4 (*c* 0.10, H<sub>2</sub>O).

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**Supporting Information Available:** Experimental procedures, compound characterization, X-ray crystallographic data, and spectral data for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(59) Due to observed broadness of some carbon signals, several <sup>13</sup>C NMR chemical shift values were obtained indirectly through <sup>1</sup>H–<sup>13</sup>C HMBC and HMQC correlations.