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Efforts Toward a Unified Kainoid Family Synthesis Approach: Unexpected Sulfinamide-Directed Conjugate Addition Results

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Abstract: A short asymmetric synthesis of an all-*syn* and all-*trans* kainoid core is reported. The synthetic route relies on the application of a new asymmetric [3 + 2] annulation reaction followed by a conjugate addition reaction to install this kainoid's three stereocenters. A surprising intramolecular conjugate addition enabled by the chiral *tert*-butylsulfinyl group residing on the 3-pyrroline nitrogen atom surpassed its expected role as a steric spectator. Efforts to outcompete intramolecular 1,4-addition by further oxidizing the sulfoxide, or use of additives, and advancement of the all-*syn* addition product to the requisite kainoid common core are detailed.

Introduction

Majority of kainoid natural products[1] share a common chiral proline core containing three contiguous stereocenters with structural diversity displayed at C4 (Figure 1). Kainic acid, whose structure was first reported more than sixty years ago,[2] is the most well-known member of this family. Other members include domoic acid,[3] isodomoic acids A-F[4] and acromelic acids A–E.[5] These structures share a common propenyl fragment (kainic acid) at C4 whose additional substitutions result in more complex chains (domoic and isodomoic acids) or rings (acromelic acids). This family of natural products display remarkable neuro-excitatory activity of the ionotropic glutamate receptors in the brain, which makes them valuable as biological tools for neurophysiological studies and promising structural starting points for developing new pain medicines.[6]

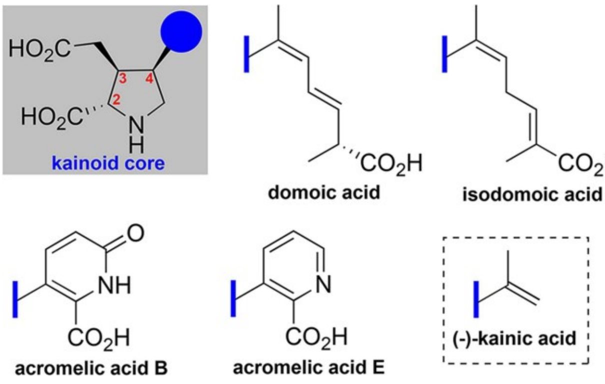
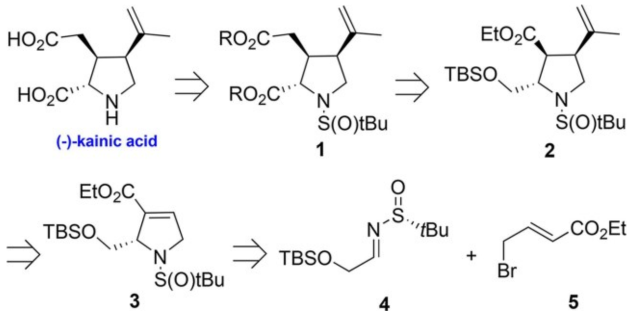


Figure 1. Examples of Kainate Amino Acid Family Members.

Inspired by the structural homology of the kainoid natural products, and the reliability and flexibility of our recently disclosed method for assembling chiral 3-pyrrolines,[7] we postulated that these kainoids could be rapidly assembled from a common precursor. To establish the feasibility of our synthetic hypothesis we chose to first study kainic acid. Although kainic acid has been synthesized numerous times,[8] it continues to serve as an attractive target. A worldwide shortage,[9] and high cost have stimulated new efforts, which is why most recent syntheses[10] are aimed at providing commercially viable routes. Our proposed asymmetric total synthesis of (−)-kainic acid is presented in Scheme 1. Chiral 3-pyrroline **3** would be assembled in a single step from Ellman imine **4** and ethyl 4-bromo crotonate (**5**). It was expected that the C3- and C4-stereocenters would be installed in a single step using a conjugate addition of a propenyl group. This key step was expected to be sterically guided by adding to the enoate from the face opposite to that of the large C2-substituent. It was anticipated that the resulting exocyclic enoate would protonate to afford the desired C3-C4 *syn*-relationship (**2**). Homologation of the ester would then lead to kainic acid following requisite deprotections of **1**.

Results and Discussion

Our initial synthetic approach is presented in Scheme 2. Assembly of the targeted chiral 3-pyrroline product (**3**) with the desired stereochemistry at C2 was easily accomplished in one



Scheme 1. Initial Kainic Acid Retrosynthetic Analysis

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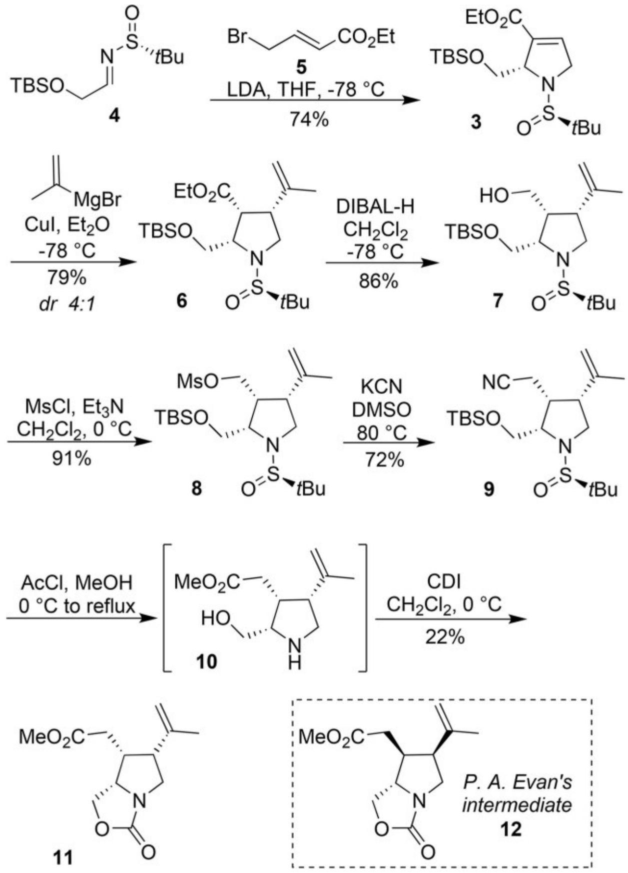
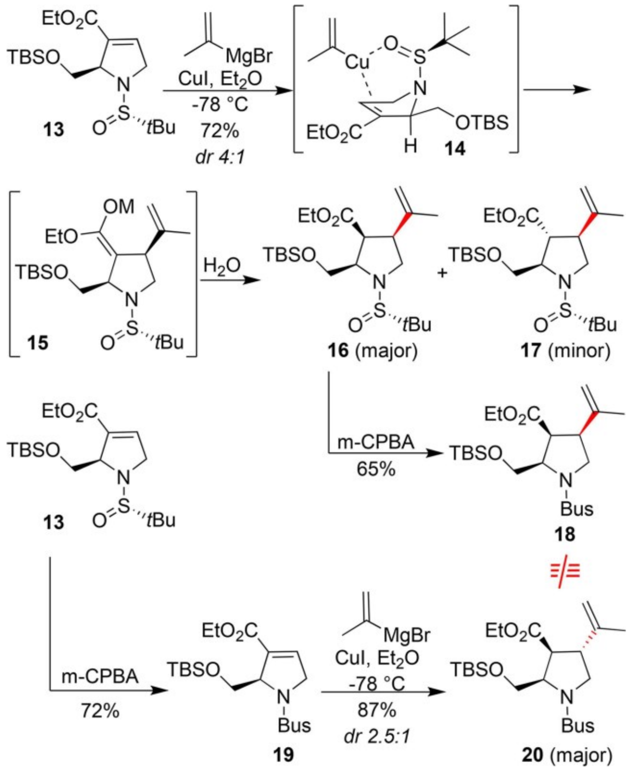


Scheme 2. Attempted Synthesis of P. A. Evan's Kainic Acid Intermediate

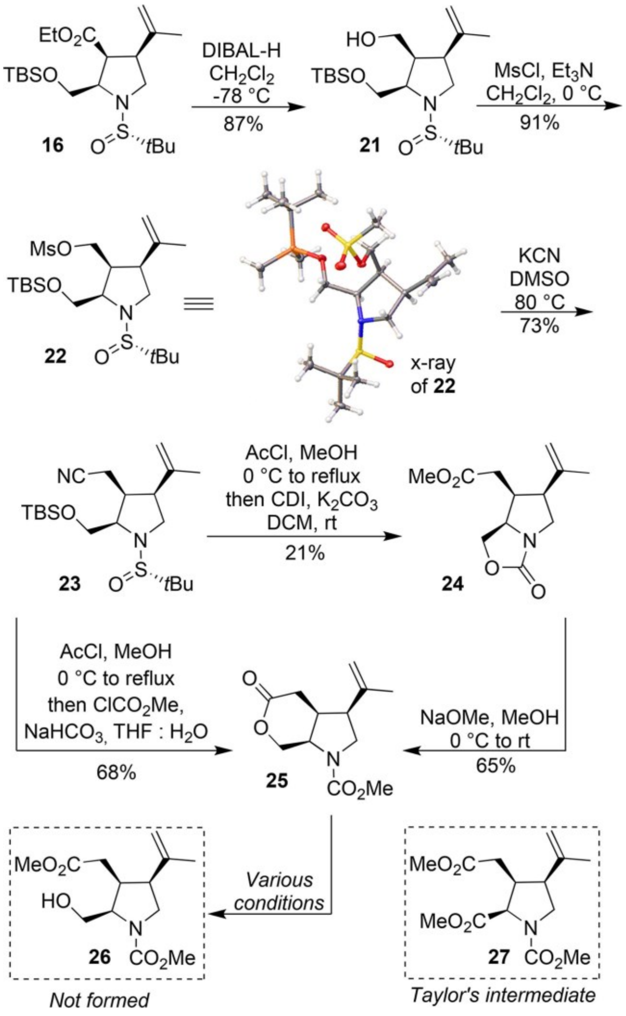
step from imine **4** and ethyl 4-bromocrotonate. We then set out to explore methods to add the propenyl group to the termini of the enoate. The first method we explored, which was a cuprate addition approach, delivered what seemed like exciting results in the form of high yields of a single diastereomer (**6**) [*dr 4 : 1*] wherein the newly installed C4- and C3-stereocenters were *syn* to each other as we had hoped. The relationship of these two new stereocenters to C2-was not clear from spectroscopic studies so we set out to advance **6** to Professor Evan's intermediate (**12**)[10d] to resolve this situation while also confirming the viability of our next few proposed steps. We considered several different approaches to homologate ester **6**, but in the end settled on the route that would be most reliable for our short-term structural confirmation goals. Toward that end, **6** was first reduced to primary alcohol (**7**) with diisobutylaluminum hydride at which point it was converted to a mesylate (**8**). Addition of potassium cyanide completed the key homologation goal by displacing the mesylate leaving group and delivering nitrile **9** in high yield. Treatment of **9** with hydrochloric acid resulted in one-pot removal of both protecting groups as well as alcoholysis of the nitrile group. Following neutralization of the reaction mixture, crude amino alcohol **10** was subjected to carbonyl diimidazole (CDI) which resulted in the formation of the targeted cyclic lactam **11** in only six reaction pots from imine **4**. To our surprise, this product did not match the spectral data for Evan's intermediate **12**. Further spectral analyses suggested that during the key conjugate addition step, the cuprate nucleophile had unexpectedly added from the same side as the C2-substitutent.



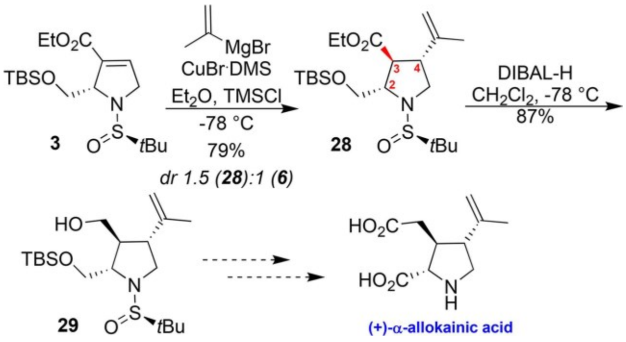
Scheme 3. Proposed Sulfinamide Directing Group Effect Model

We postulate that the reason for the unexpected C2/C4-*cis* reaction outcome in the cuprate addition step is that the sulfinamide group coordinates to the cuprate thus delivering the propenyl group in an intra- instead of an inter-molecular fashion. This directing group postulate is graphically presented in Scheme 3. Over the last few decades, a variety of functional groups have been shown to be capable of directing organocuprate reagents.[11] The closest example to ours in the literature is from Professor Ellman,[12] who proposed a directing role for similar chiral imines when treated with a cuprate reagent in the presence of an additive. It is worth noting, that interest and applications of chiral sulfoxides as directing groups for asymmetric catalysis applications is steadily on the rise.[13] To further support our directing group hypothesis, we oxidized the proposed chiral sulfoxide directing group of **13** (made using the enantiomer of **4**) to a sulfone (SO_2t-Bu = Bus, **19**). Treatment of **19** with the same cuprate conjugate addition conditions, afforded **20** as the major product [*dr 2.5 : 1*]. Comparison of this product with the one obtained from oxidizing **16** to its Bus-protected variant **18** revealed that they are not the same thus lending further support for the sulfoxide directing group hypothesis. Detailed NMR-analysis of **20** confirmed it has the stereochemistry shown, which means the approach of the cuprate nucleophile was sterically controlled resulting in the originally desired C4-stereochemistry. This experiment lends further support to the sulfoxide directing group hypothesis.

Despite the unexpected influence of the directing group, our kainic acid synthetic plans we argued could still be realized. One of the key advantages of our new chiral 3-pyrroline method is that either enantiomeric series of the product can be accessed by changing the configuration of the imine auxiliary. This coupled with the well-established fact that the C2-stereocenter of diesters of kainic acid can be epimerized[14] from the unnatural (*R*)- to the natural (*S*)-configuration means that **16** (Scheme 4), could be advanced to the natural product. Reduction of the ester followed by mesylation yielded **22** in excellent overall yield. Mesylate **22** also provided us with high quality crystals that allowed us to conduct an x-ray crystallography analysis,[15] which confirmed its relative and absolute configuration as that shown in Scheme 4. Displacement of the mesylate with potassium cyanide afforded nitrile **23**, which was then converted into an amino alcohol ester using the one pot global deprotection procedure we had developed. Treatment of the crude amino alcohol with carbonyl diimidazole (CDI) afforded carbamate **24**. Our hope was that following opening of the carbamate, that oxidation of the primary alcohol followed by esterification would yield a diester product (**27**) from Professor Taylor's total synthesis.[16] Unfortunately, although we were able to easily open the carbamate, in all cases instead of making **26** we formed lactone **25**, which has been shown to be a dead end for kainic acid by Taylor.[17] Our own lactone ring opening attempts also met the same fate and did not produce desired alcohol **26**.



Scheme 4. 2nd Kainic Acid Synthesis Approach



Scheme 5. Effect of Additive of C3-stereochemistry in Cuprate Addition Step

Finally, although the sulfinamide chiral auxiliary is controlling and setting the C4-stereochemistry we wondered if the intermediate copper enolate stereochemistry could be manipulated by use of additives to deviate from the all-*syn* stereochemistry to all-*trans*. If possible, this would potentially pave the way for the asymmetric total synthesis of (+)-α-allokainic acid,[18] which has this exact stereochemical arrangement (Scheme 5). Silyl chlorides are well established as useful additives in organocuprate chemistry.[19] We screened several silyl chlorides (TMSCl, TBSCl, TIPSCl and TBDPSCl) in the presence of CuI or CuBr·DMS as well as propenyl magnesium bromide. In all cases, the expected cuprate addition took place with C4-stereochemistry firmly set as *syn* with respect to C2. The stereochemical outcome at C3 could indeed be reversed, with best results obtained using TMSCl and CuBr·DMS, which afforded the all-*trans* product **28** in 47% isolated yield and modest preference over the all-*cis* product (**6**) [*dr 1.5 : 1*].

Conclusions

In summary, we have developed a novel asymmetric route to an all-*syn* kainoid core from readily available starting materials. The pyrrolidine core along with its three stereocenters is assembled in only two steps using our chiral pyrroline annulation reaction coupled with an unexpected sulfinamide directed cuprate addition reaction, which we predict can serve as a guide future sulfinamide guided cuprate additions. Furthermore, we demonstrated that the protonation step of the conjugate addition step could be impacted by use of silyl additives, opening a potential route to (+)-α-allokainic acid. Future efforts are focused replacing the ester functionality with an alternate electron withdrawing group that will enable us to suppress directing group effects and streamline sequence by avoiding intermediate redox and homologation steps.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: kainic acid · annulation · anionic cascade · asymmetry · sulfonamide

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