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Total Synthesis of (±)-Kainic Acid with an Aza-[2,3]-Wittig Sigmatropic Rearrangement as the Key Stereochemical Determining Step

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A flexible route to the kainoid skeleton is exemplified by the synthesis of (±)-kainic acid from 3-butyn-1-ol. The route relies on the aza-[2,3]-Wittig sigmatropic rearrangement to efficiently install the relative stereochemistry between C2−C3. The C4 stereocenter was derived from a diastereocontrolled iodolactonization. The aza-[2,3]-Wittig rearrangement potentially allows structural diversity at C3 and the displacement of the tosyloxy group with retention of stereochemistry allows structural diversity at C4. The *trans*-C2 carboxylic acid functional group was found to be the most important for retention of stereochemistry at C4 upon treatment with a higher order cyano cuprate reagent.

Introduction

The kainoid amino acids are a group of nonproteinogenic pyrrolidine dicarboxylic acids of which (−)-kainic acid (**1**) is the parent member. The kainoids exhibit a wide variety of biological properties and have been used as insecticides, anthelmintic (anti-intestinal worm) agents, and most prominently neuroexcitatory agents. Their potent neuroexcitatory activity, which leads to specific neuronal death in the brain, is attributed to their action as conformationally restricted analogues of the neurotransmitter glutamic acid. The nature and stereochemistry of the unsaturated C4 substituent plays a crucial role in binding and functional activation at the active site.[1] Interest in the development of these types of molecules as neuroprotective therapeutics[2] and pesticides[3] demands new, flexible methods for their synthesis. There is also great interest in the synthesis of kainic acid derivatives as some have been shown to be more potent than the natural molecules themselves.[4] There have been numerous asymmetric[5] and racemic[6] syntheses of kainic acid over the past 20 years. However, very few of these allow the convergent synthesis of a wide range of different kainoids through a late-stage common intermediate. The introduction of C4 substituents by displacement of *trans*-4-tosyloxy-L-prolines, with retention of stereochemistry, has been reported.[7] This strategy was applied to the synthesis of C4 acromelic acid congeners,[4] which are related members of the kainic acid family. To the best of our knowledge kainic acid itself has not been synthesized by this route. In this paper we show the use of the aza-[2,3]-Wittig rearrangement in deriving the initial stereochemistry needed for the stereocontrolled synthesis of an advanced tosyloxy intermediate **5** (Scheme 1) and its conversion to (±)-kainic acid.

The stereochemical determination step would be derived from aza-[2,3]-Wittig rearrangement of achiral **2**, giving the desired trans stereochemistry according to our transition state model and previous work.[8] By analogy

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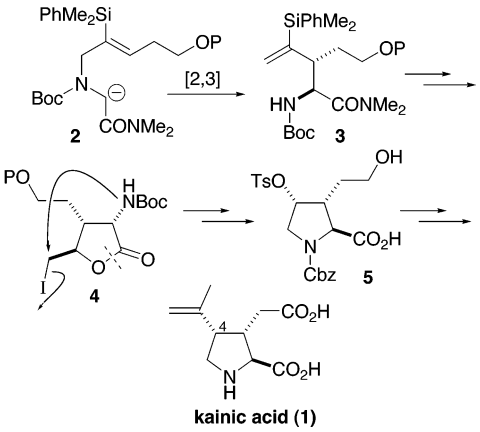
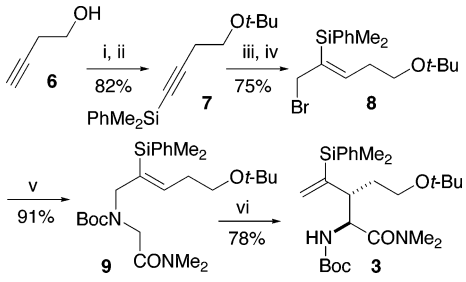
SCHEME 1. Synthetic Plan



SCHEME 2[a]



[a] Reagents: (i) isobutene, amberlyst 15; (ii) *n*-BuLi, $PhMe_2SiCl$; (iii) DIBAL; MeLi, $(HCHO)_n$; (iv) PPh_3, Br_2, Et_3N; (v) KH, $BocNHCH_2CONMe_2$; (vi) LDA.

to the work of Yoshida et.al.[9] on the iodolactonization of α- and α,*β*-substituted *γ*,*δ*-unsaturated amides, 1,3-stereochemical transfer would ensure the formation of the C4-oxygen stereocenter in **4**. Base-promoted rearrangement according to the methodology of Ohfune et al.[10] would provide the proline skeleton of kainic acid. We have used this strategy before in the synthesis of the nonproteinogenic amino acid (±)-(2*S*,3*R*,4*R*)-4-hyroxy-3-methylproline, which possesses a similar carbon core to kainic acid.[11] The present synthesis requires further manipulation to tosyloxy derivative **5** to give the late-stage intermediate required for the synthesis of kainic acid via retentive displacement with an isopropenyl nucleophile.

Results and Discussion

The synthesis of the aza-[2,3]-Wittig precursor began with commercially available 3-butyne-1-ol (**6**, Scheme 2). The hydroxyl function would ultimately become the C3 carboxyl group in **1**, but it needed protecting throughout most of the synthesis. We required a robust protecting group that would withstand the high concentration of DIBAL required for hydroalumination to **8**. Although the *tert*-butyldimethylsilyl group is normally stable to metal hydride reagents, it is cleaved by DIBAL at room temperature.[12] We did investigate the use of the bulky triisopropylsilyl group,[13] and although this withstood the harsh hydroalumination conditions, it proved problematic in the protodesilylation of the aza-[2,3]-Wittig product **2** later on in the synthesis. We decided to use the *tert*-butyl ether as a protecting group as it is robust, cheaply attached with use of isobutene, and removed under a variety of mild conditions.[14] Protection of **6** as its *t*-Bu ether[15] followed by deprotonation of the terminal alkyne and quenching with chlorodimethylphenylsilane gave fully protected **7** in 82% yield over two steps (Scheme 2). Regio- and stereospecific hydroalumination of the alkyne, treatment with MeLi to form the ate complex, and quenching with paraformaldehyde[16] gave the allylic alcohol, which was readily converted to bromide **8** in 75% yield over two steps. The rearrangement precursor was then completed by coupling **8** with the potassium anion of *N*-Bocglycine *N*,*N*-dimethylamide to give **9** in 91% yield. The aza-[2,3]-Wittig rearrangement was induced by using LDA (1.4 equiv) at −78 °C with warming to 0 °C for 2 h to give the pivotal unnatural amino acid derivative **3** (P = *t*-Bu) in 78% yield. The crude ^1H NMR revealed only one rearranged product although a small amount (0.6%) of the minor diastereoisomer was isolated after column chromatography. We were confident at this stage that the sense of diastereoselection would be identical with simpler analogues which had been proved by single-crystal X-ray crystallography and was therefore assigned anti as drawn (Scheme 2).[8,11] This assignment was later verified by conversion to (±)-kainic acid (**1**).

Protodesilylation was achieved by a slight alteration of conditions previously reported by us and required an optimum 1.5 equiv of water in the first step of a two-step process that furnished silanol **10** and alkene **11** as a 1:2 mixture in the crude material. Direct treatment with excess TBAF gave **11** in 59% overall yield. This protodesilylation reaction is still under investigation.[17] Iodolactonization with I_2 in DME/H_2O gave a 7:1 mixture of **4** (P = *t*-Bu):**12** in 74% and 11% isolated yields, respectively (Scheme 3). The major diastereoisomer was predicted to be **4** based upon the work of Yoshida and was verified by comparison of selected one-dimensional nOe data. Vicinal protons with a trans relationship around the lactone ring gave a nOe enhancement of <3%, whereas those with a cis relationship gave enhancements of >9%.[18] Deprotection of the amine substituent followed by base-induced ring opening of the lactone gave the proline skeleton **13** after 5-*exo*-tet cyclization in 86% yield.

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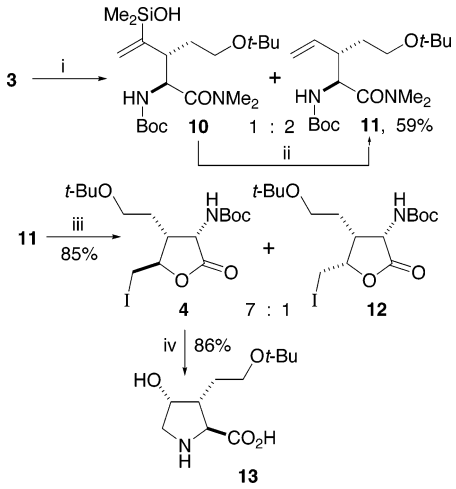
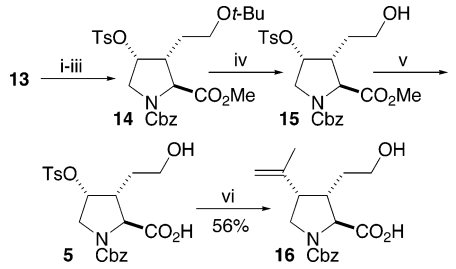
(18) See the Supporting Information for details of irradiations and enhancements. The stereochemical assignment was also verified by the completion of the synthesis.

SCHEME 3[a]



[a] Reagents: (i) *t*-BuOK, 18-crown-6, H_2O; (ii) TBAF; (iii) I_2; (iv) TFA; KOH.

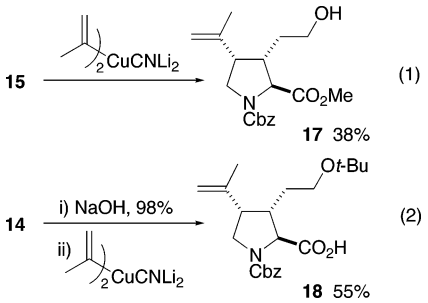
SCHEME 4[a]



[a] Reagents: (i) BCN, 98%; (ii) CH_2N_2, 98%; (iii) Ts-Imid, MeOTf, Me-Imid, 83%; (iv) TFA, 96%; (v) 0.5 M NaOH, 98%; (vi) $[CH_2{=}C(CH_3)]_2CuCNLi_2$, 56%.

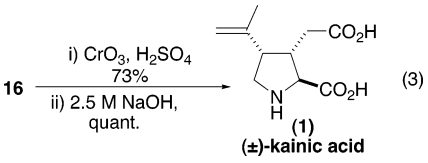
Completion of the synthesis required orthogonal protecting group manipulation to obtain the alkylation precursor **5**. Reaction of **13** with BCN[19] in THF/H_2O (Scheme 4) gave the Cbz-protected amine (98%), which was then esterified with CH_2N_2 (98%). Tosylation of the C3 hydroxyl with TsCl gave disappointing yields; however, use of 1-(toluenesulfonyl)-3-methylimidazolium triflate[20] gave the desired tosylate **14** in 83% yield. Removal of the long-serving *tert*-butyl protecting group with TFA gave **15** (96%), which was saponified with NaOH (98%) to give our key intermediate **5** in 75% overall yield from **13**.

We initially attempted the substitution reaction of **5** with a lower order Gilman type diisopropenyl cuprate by analogy to the work of Shirahama.[4] Even after prolonged reaction periods at room temperature no product formation was observed, only degradation of the starting material. We had more success with a higher order diisopropenyl cyano cuprate, generated from CuCN and 2-lithiopropene. This reaction was very sensitive to reaction conditions and care had to be taken to rigorously dry the CuCN and perform the reaction under a positive pressure of argon. Optimum reaction conditions involved treatment of **5** with 5 equiv of the higher order cuprate reagent at −78 °C followed by warming to room temperature for 2 h to give a 56% yield of the desired product. Retention of stereochemistry was verified by one-dimensional nOe experiments.[18] In an attempt to increase the yield and probe which functional groups were responsible for retention of stereochemistry in this step, the cuprate reaction was conducted on protected analogues of **16**. Treatment of fully protected tosylate **14** under identical substitution conditions gave only inseparable mixtures of unidentified products. Subjection of **15** to identical reaction conditions gave isopropenyl-substituted compound **17** in 38% isolated yield along with an inseparable mixture of other unidentifiable products (eq 1). Retention of stereochemistry was again verified by one-dimensional nOe enhancements.[18] Treatment of **14** with NaOH gave the carboxylic acid derivative in 98% yield, which upon treatment with our optimized substitution conditions gave isopropenyl product **18** in 55% yield (eq 2). Retention of stereochemistry at C3 was verified by removal of the *t*-Bu protecting group to give **16**.



Whether the hydroxyl group was protected, when in the presence of the carboxylic acid function, was immaterial to the yield and selectivity of the reaction. Participation of the C2 acid group was one of the possible scenarios suggested for lithium diphenylcuprate retentive displacement of *trans*-4-tosyloxy-L-proline.[7] From our limited study it would appear that the ester function, as well as the carboxylic acid function, can assist this retentive displacement reaction. The carboxylic acid function gives a higher yield. Although none of the intermediate lactone was isolated, we invoke participation of the C2 carboxyl group in the substitution reaction.

Completion of the synthesis involved oxidation with Jones' reagent, followed by removal of the Cbz protecting group with aqueous NaOH and purification by ion exchange chromatography, which gave (±)-kainic acid (**1**) in 73% yield from the substitution product **16** (eq 3). The synthetic material displayed identical ^{1}H NMR data to an authentic sample and gave a homogeneous ^{1}H NMR spectrum when co-mixed.



We have achieved a novel total synthesis of (±)-kainic acid in 18 steps starting from 3-butyne-1-ol. The silicon-assisted aza-[2,3]-Wittig sigmatropic rearrangement was key in defining the C2−C3 relative stereochemistry with the final C4 stereocenter being derived from a diastereo-

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controlled iodolactonization We believe that this route could be useful for synthesizing other kainoid analogues. The aza-[2,3]-Wittig rearrangement offers the opportunity of structural diversity at C3, which, coupled with the retentive displacement of the C4 tosyloxy substituent with different nucleophiles, opens up many opportunities for uncharted structural diversity in this class of therapeutic compounds. Work is currently underway to control absolute stereochemistry in the aza-[2,3]-Wittig sigmatropic rearrangement, which will lead to the synthesis of enantiomerically pure kainic acid derivatives.

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Supporting Information Available: Syntheses and spectroscopic data of all compounds, including selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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