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Enantioselective Total Synthesis of (−)-α-Kainic Acid

Andreas Farwick and Günter Helmchen*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

g.helmchen@oci.uni-heidelberg.de

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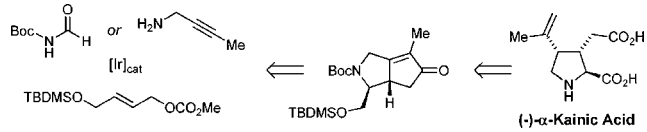
ABSTRACT



An enantioselective total synthesis of (−)-α-kainic acid is described. Key steps are an Ir-catalyzed allylic amination with a propargylic amine to provide an enyne and a diastereoselective intramolecular Pauson−Khand reaction. Subsequent steps involve a Baeyer−Villiger reaction, reduction of the resulting lactone, and direct Jones oxidation of a silyl ether.

In 1953 (−)-α-kainic acid (Figure 1) was first isolated from the marine alga *Digenea simplex*.[1] Kainic acid is the structurally simplest member of the kainoid family[2] of alkaloids. These nonproteogenic amino acids show anthelmintic[3] and neurotransmitting activities.[4] (−)-α-Kainic acid is being widely used as a tool in neuropharmacology[5] for mimicry of various stages of neuronal disorders such as epilepsy,[6] Alzheimer's disease, and Huntington's chorea.[7] A shortage in the commercial extraction of natural kainic acid led to an impediment of neuroscience.[8]

As a consequence, the synthesis of (−)-α-kainic acid has received particular attention, and more than 20 total syntheses have been reported.[9−11] Most of the syntheses start with an enantiomerically pure compound from the chiral pool, for example, serine or glutamic acid. The number of true enantioselective syntheses, i.e., with an achiral compound as starting material, is small; still smaller is the number of syntheses based on enantioselective catalysis.[10]

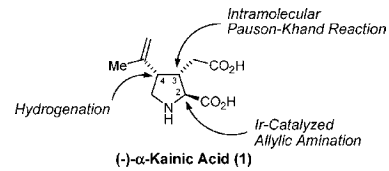


Figure 1. Generation of the stereogenic centers of (−)-α-kainic acid (**1**).

We herein present a concise *enantioselective* total synthesis of (−)-α-kainic acid. The enantiomeric purity of the target of 99% ee is based on the Ir-catalyzed allylic amination, which provides for the chirality center C2 (Figure 1 and Scheme 1). Chirality centers C3 and C4 were introduced by an intramolecular Pauson−Khand reaction and catalytic hydrogenation, respectively.

The Pauson−Khand reaction has been employed in syntheses of (−)-α-kainic acid.[11] However, the reported syntheses are complicated by low diastereoselectivity in the

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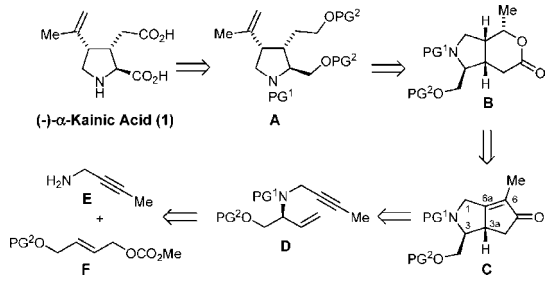
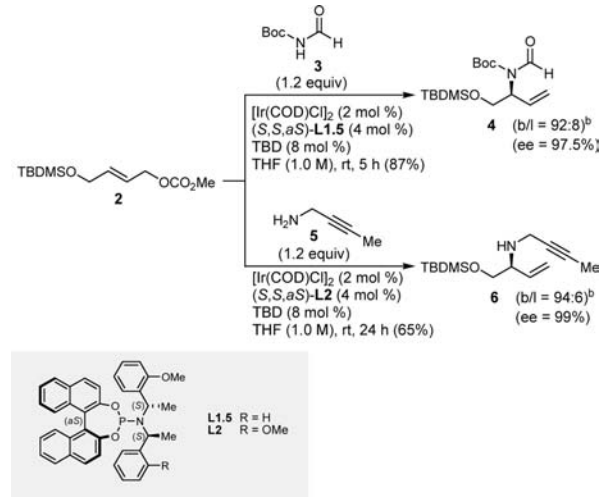
Scheme 1. Retrosynthetic Analysis



Pauson−Khand step,[11a] interchange of protecting groups,[11b] or very high numbers of steps.[11c] The protecting group at nitrogen of intermediate **D** of Scheme 1 is of crucial importance for the diastereoselectivity with respect to centers C3 and C3a. In a series of tests, we found that an *N*-Boc group generally gave rise to high diastereoselectivity.[12] This group appeared also compatible with all other planned synthetic operations. The Si(*t*-Bu)Me_2 (TBDMS) group was selected as the *O*-protecting group because of the possibility to directly oxidize a $CH_2OSi(t\text{-Bu})Me_2$ group to a carboxyl group.[13]

The Ir-catalyzed allylic amination has been developed into a reliable tool over the past few years.[14] In the present synthesis, one would like to carry out a substitution at the carbonate **2**[15b] (Scheme 2) using *N*-Boc-but-2-inylamine as nucleophile. However, so far conditions have not been developed that allow *N*-alkyl-amides to be employed. Therefore, two related nucleophiles were probed.

Scheme 2. Ir-Catalyzed Allylic Amination[a]



[a] TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [b] The term b/l denotes the ratio of branched and linear product of the allylic amination.

The *N*,*N*-diacylamine **3** is an ammonia equivalent, which is known to provide both excellent regioselectivity, i.e., a high ratio of branched to linear substitution product, as well as high enantiomeric excess.[15] The reaction with carbonate **2** under "salt-free" conditions[15a] gave the branched product **4** in 87% yield with enantiomeric purity of 97.5% ee (Scheme 2).

Amines are also excellent nucleophiles for the Ir-catalyzed allylic amination.[16] In the present case, the primary amine but-2-ynylamine (**5**) appeared as a logical choice. However, so far no example of a reaction with a propargylic amine has been reported.[17] Accordingly, we were pleased to find that the reaction proceeded with a very good regioselectivity, ratio b/l = 94:6, and an excellent enantiomeric excess of 99% (Scheme 2).

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(12) We have tested Ts, SO_2t-Bu, Boc, and Cbz as *N*-protecting groups. Excepting Boc, in all cases the diastereoselectivity was in the range of 66:34 to 82:18. This observation is in accordance with results described in: Yoo, S.-E.; Lee, S.-H.; Jeong, N.; Cho, I. *Tetrahedron Lett.* **1993**, *34*, 3435–3438, and in ref 11b.

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(15) Ir-catalyzed allylic amination with *N*,*N*-diacylamines: (a) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546–5549. (b) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331–3350. (c) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 7094–7098.

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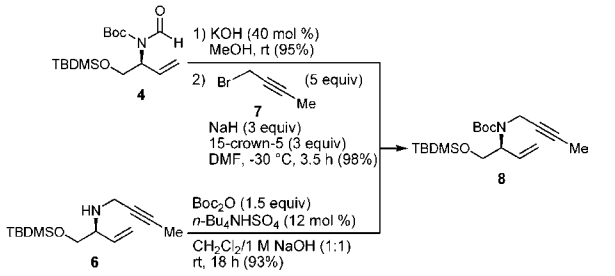
Scheme 3. Synthesis of the 1,6-Enyne **8**



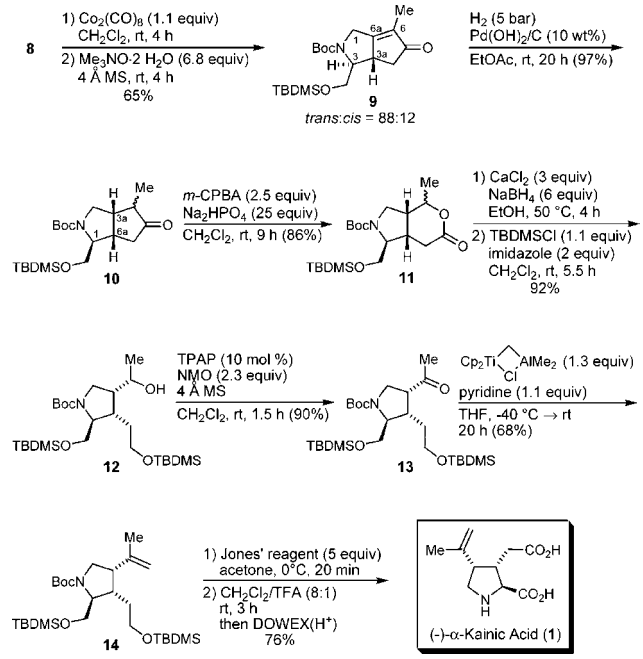
The 1,6-enyne **8** was prepared from both **4** and **6** (Scheme 3). The formyl group of **4** was removed with methanol and a catalytic amount of KOH. Subsequent *N*-alkylation with 1-bromobut-2-yne (**7**) needed careful control of reaction conditions in order to avoid a shift of the double bond; alkylation at −30 °C in DMF in the presence of 15-crown-5 turned out to give good results. No reaction occurred in the absence of crown ether. In the second route, Boc-protection of **6** was carried out with a biphasic mixture of CH_2Cl_2 and 1 M NaOH in the presence of the phase transfer catalyst *n*-Bu_4NHSO_4. The enyne **8**, the substrate for the Pauson−Khand reaction, was obtained in high yield.

The further steps of the total synthesis of (−)-α-kainic acid are described in Scheme 4. A protocol of the intramolecular Pauson−Khand reaction[18] using molecular sieves 4 Å as additive[19] was followed for generation of the key cyclopentenone intermediate **9** from the 1,6-enyne **8**. The reaction proceeded with 65% yield and a trans:cis diastereomer ratio of 88:12 with respect to the moiety C3/C3a. Pure *trans*-**9** was isolated by chromatography in 57% yield.

Catalytic hydrogenation of the tetrasubstituted olefin **9** with H_2/$Pd(OH)_2$/C gave **10** as a 60:40 mixture of epimers. As the newly formed stereogenic center would be destroyed later, separation of the diastereomers was not necessary. Subsequent Baeyer−Villiger rearrangement[20] with *m*-CPBA, buffered with Na_2HPO_4, in CH_2Cl_2 gave the lactone **11** in 86% yield.

As opening of lactones of this type with methoxide or MeOH/Et_3N is known to proceed with low yield because of

Scheme 4. Completion of the Total Synthesis of (−)-α-Kainic Acid (**1**)[a]



[a] TPAP: tetrapropylammonium perruthenate.

the reversibility of the reaction,[9v] we decided to reduce the lactone. This was cleanly effected with in situ formed $Ca(BH_4)_2$[21] in ethanol to give the corresponding dialcohol, which in crude form was reacted with *t*-$BuMe_2SiCl$ (TBDMSCl) selectively at the primary OH group to give the monoalcohol **12** in 92% yield. Ley−Griffith oxidation[22] furnished the methylketone **13**, which was transformed under nonbasic conditions into the olefin **14** by reaction with Tebbe's reagent.[23] No epimerization occurred in the build-up of the propenyl group.

Next, oxidation of **14** to the dicarboxylic acid and *N*-deprotection were required. Evans et al. have demonstrated that TBDMS ethers of primary alcohols can be directly oxidized with Jones' reagent to give carboxylic acids.[13] However, the oxidation of the silyl ether **14** under standard conditions proceeded with partial cleavage of the Boc group to give mixtures of chromium salts from which kainic acid could not be obtained in reasonable yield. Extensive experimentation with careful control of temperature, concentration, and amount of oxidant led to conditions mainly yielding *N*-Boc-kainic acid, which could be isolated free of chromium impurities. Despite the sensitivity of the 2-propenyl moiety to acid, *N*-deprotection under carefully controlled conditions proceeded smoothly. Analytically pure (−)-α-kainic acid (**1**) was obtained after ion exchange chromatography (DOWEX

(17) A large number of highly selective Ir-catalyzed allylic aminations with *N*-tosyl-propargylamines have been carried out by S.-L. You and coworkers at the Shanghai Institute of Organic Chemistry, private communication of Prof. S.-L. You. In our group, Ir-catalyzed alkylations of cinnamyl methyl carbonate with the pronucleophiles R−C≡C−CH_2−$CH(COOMe)_2$, R = H and Me, have been studied (ligand **L2**). In the case R = Me, excellent results were obtained (98.5% ee), in the case R = H the reaction proceeded, but the ee was low, only 12%.

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50WX8) in 76% yield over two steps; the spectral data matched those reported for the natural product.[24]

Overall, our synthesis from the carbonate **2** via **4** or **6** required 13 or 12 steps and gave a total yield of 16% or 12%, respectively.

In summary, we are reporting a straightforward enantioselective total synthesis of (−)-α-kainic acid (**1**). Key steps are an Ir-catalyzed allylic amination with a propargylic amine, which proceeded with very high enantio- and regioselectivity, and an intramolecular, highly diastereoselective Pauson−Khand reaction. No exchange of protecting groups was required.

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Supporting Information Available: Experimental details including spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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