



An Enantioconvergent Route to (–)-Kainic Acid

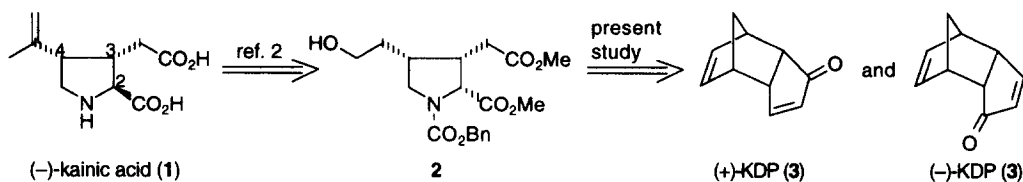
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Abstract: A new stereocontrolled route to (–)-kainic acid, the representative of the kainoid amino acids and exhibiting insecticidal, anthelmintic and neuroexcitatory properties, has been devised in an enantioconvergent way using either (+)- or (–)-ketodicyclopentadiene as the starting material by employing a concurrent retro-Diels-Alder reaction and intramolecular ene reaction as the key step.
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The kainoid amino acids have attracted considerable interest because of their pronounced insecticidal, anthelmintic and neuroexcitatory properties.¹ Among these properties, the neuroexcitatory activity is attributed to their *trans*-C-2/C-3:*cis*-C-3/C-4 structure and the functionality on the C-4 center besides 2-carboxy-3-carboxymethyl functionalities. Accordingly, an efficient enantiocontrolled procedure being capable of producing the appropriate 2,3,4-trisubstituted pyrrolidines carrying a versatile C-4 functionality has been sought. We report here a new stereocontrolled route to (–)-kainic acid (**1**) in a formal sense by the synthesis of the key intermediate **2** carrying a versatile 4-(2-hydroxyethyl) group starting either from the (+)- or (–)-enantiomer of optically pure ketodicyclopentadiene^{3,4} (KDP) (**3**) by employing a concurrent one-pot retro-Diels-Alder reaction and intramolecular ene reaction as the key step (**Scheme 1**).

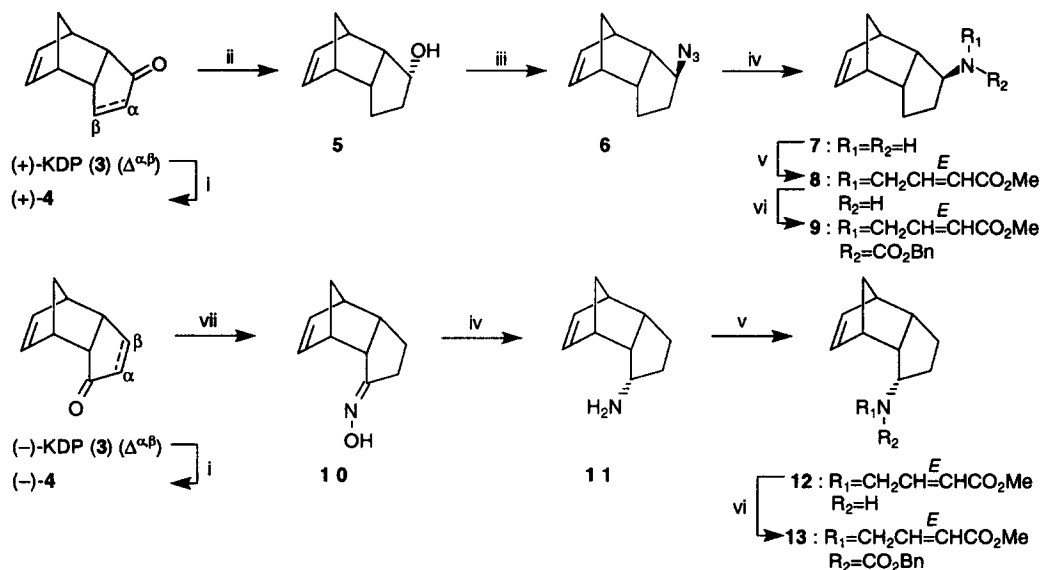


Scheme 1

(+)-KDP [(+)-**3**] (>99% ee) was transformed stereoselectively into the *endo*-alcohol⁵ **5**, mp 96 °C, $[\alpha]_D^{28}$ –13.1 (*c* 0.5, CHCl₃), in 88% yield *via* the (+)-ketone⁶ (+)-**4**. The Mitsunobu reaction⁷ of **5** with diphenylphosphoryl azide (DPPA) gave the *exo*-azide **6**, $[\alpha]_D^{27}$ +70.4 (*c* 1.0, CHCl₃), with inversion which was sequentially transformed into the *exo*-carbamate **9**, $[\alpha]_D^{25}$ +49.1 (*c* 1.0, CHCl₃), having the *N*-(*E*-3-

ethoxycarbonyl-2-propenyl) group via the *exo*-primary amine **7** and the *exo*-secondary amine **8**. Overall yield of **9** from **5** was 44% in four steps.

On the other hand, (–)-KDP [(–)-**3**] (>99% ee) was transformed into the single oxime **10**, $[\alpha]_D^{27} -279.5$ (*c* 1.3, CHCl₃), via the (–)-ketone⁶ (–)-**4**. On sequential stereoselective reduction, *N*-alkylation, and carbamoylation, **10** furnished the *endo*-carbamate **13**, $[\alpha]_D^{27} -83.8$ (*c* 1.6, CHCl₃), via the *endo*-primary amine **11** and the *endo*-secondary amine **12**. Overall yield of **13** from (–)-**3** was 49% in five steps (Scheme 2).



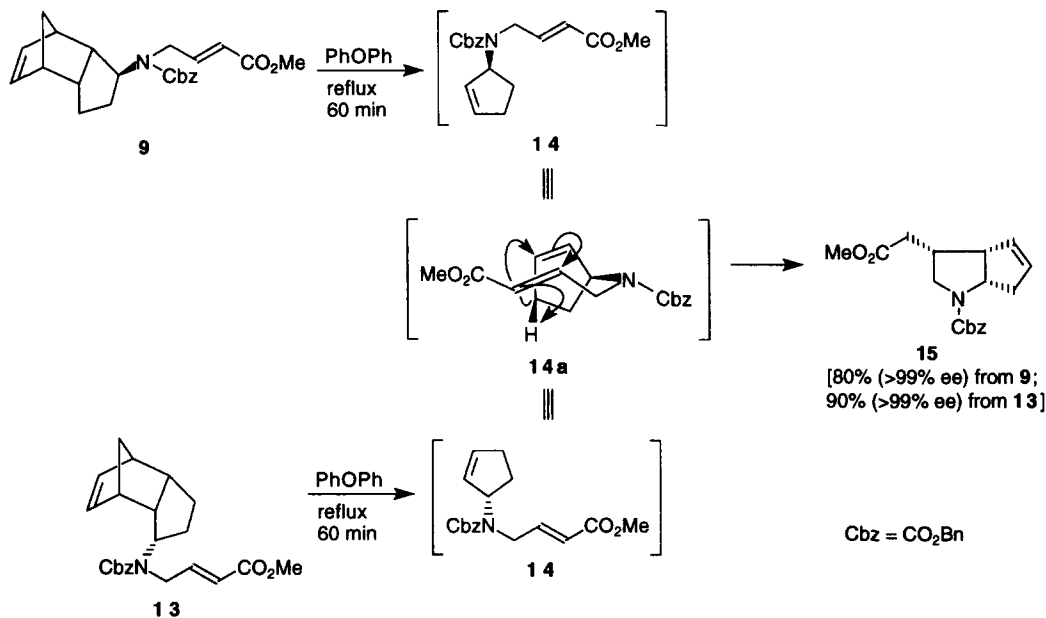
Scheme 2

Reagents and conditions: i, Zn, AcOH-EtOH (1:4), reflux [97% for (–)-**4**]; ii, NaBH₄, MeOH, –78 °C [88% from (+)-**3**]; iii, DPPA, (NCO₂Et)₂, PPh₃, THF, 0 °C ~ room temp. (94%); iv, LiAlH₄, THF, room temp.; v, BrCH₂CH=CHCO₂Me, Et₃N, DMF, 0 °C; vi, ClCO₂Bn, NaH, DMF, –20 °C [47% for **9** from **6** and 49% for **13** from (–)-**3**]; vii, NH₂OH·HCl, pyridine, room temp. (97%).

Having obtained the *exo*-**9** and the *endo*-**13** diastereomers, we next examined the thermolysis of these compounds in hot diphenyl ether. Since we had learned that the retro-Diels-Alder reaction of certain substrates having a bicyclo[2.2.1]heptene system relating to **9** and **13** was best carried out in diphenyl ether at boiling point⁸ (~260 °C), we expected both of these would form the same monocyclic carbamate **14** having a 1,6-diene system which further would undergo the intramolecular ene reaction⁹ under the same conditions to give the bicyclo product **15** having a trisubstituted pyrrolidine framework.

When the *exo*-**9** was heated in diphenyl ether at refluxing temperature, the reaction terminated within 60 min to give rise to the bicyclic product **15**, $[\alpha]_D^{27} +95.8$ (*c* 1.0, CHCl₃), in 80% yield as the single isomer as expected. On the same treatment, the *endo*-diastereomer **13** afforded the same bicyclic product **15**, $[\alpha]_D^{30} +94.7$ (*c* 1.1, CHCl₃), in 90% yield as a single isomer. The optical purities of the product **15** from both **9** and **13** were determined to be >99% ee by hplc using a chiral column (CHIRALCEL OD, elution with 5% *i*-

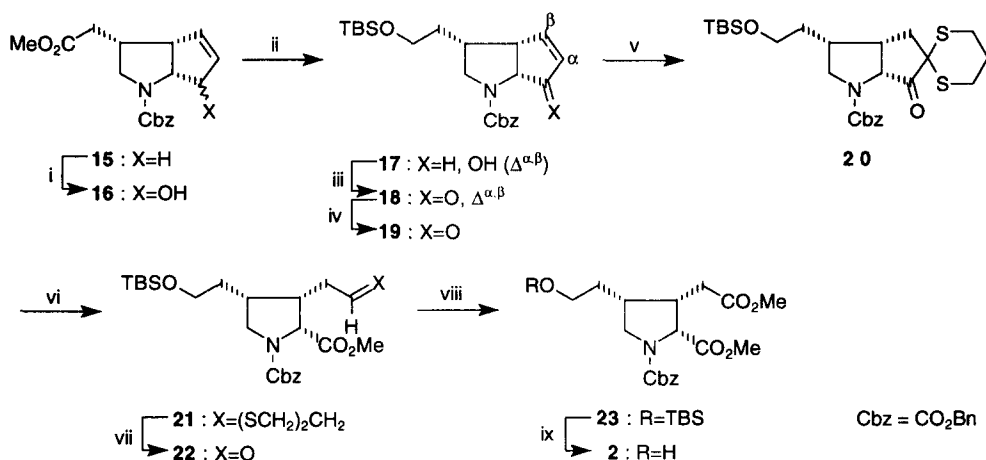
PrOH/hexane), indicating that the original chiral integrity of the precursor carbamates was preserved under these thermal conditions. The relative stereochemistry of **15** was determined to be the all-*cis* configuration as shown by facile iodolactone formation (single product in 73% yield) when the carboxylate generated from **15** by saponification was treated with iodine in acetonitrile¹⁰; its absolute stereochemistry, however, was determined after converting it into the key intermediate **2** (see below). These findings led us to conclude that the intramolecular ene reaction of the transient 1,6-diene **14** took place in a stereospecific manner taking the most unstrained transition state **14a** to afford the all-*cis* product **15** (Scheme 3).



Scheme 3

In order to obtain the key intermediate **2** of (–)-kainic acid (**1**), the ene product **15** was first treated with selenium(IV) oxide in the presence of formic acid¹¹ to give the allylic alcohol **16** in 68% yield as a diastereomeric mixture. On sequential hydride reduction, selective *O*-silylation, manganese(IV) dioxide oxidation, and the cuprate-mediated 1,4-reduction,¹² **16** furnished the bicyclic ketone **19**, $[\alpha]_D^{27} +106.6$ (*c* 1.3, CHCl₃), in 58% overall yield *via* the silyl ether **17** and the enone **18**, $[\alpha]_D^{27} +124.0$ (*c* 1.6, CHCl₃). The ketone **19** was transformed into the α-diketone monothioacetal¹³ **20**, $[\alpha]_D^{21} -21.8$ (*c* 1.1, CHCl₃), in 85% yield which was cleaved under basic conditions¹³ to give the dithiane **21**, $[\alpha]_D^{28} -7.1$ (*c* 1.0, CHCl₃), in 60% yield after esterification. Hydrolysis of the dithiane group¹³ of **21** afforded the aldehyde **22**, $[\alpha]_D^{27} +19.2$ (*c* 0.7, CHCl₃), in 90% yield which, on oxidation with a mixture of iodine and potassium hydroxide in methanol,¹⁴ furnished the key intermediate **2**, $[\alpha]_D^{31} +13.1$ (*c* 0.3, CHCl₃) [lit.^{2b}: $[\alpha]_D^{27} +11.7$ (*c* 0.5, CHCl₃)], in 61% yield after desilylation¹⁵ of the resulting monocyclic silyl ether **23**, $[\alpha]_D^{28} +32.8$ (*c* 0.1, CHCl₃) (Scheme 4).

As we have obtained^{2a} (–)-kainic acid (**1**) from **2**, the present synthesis constitutes a formal enantio-convergent synthesis starting from both (+)- and (–)-enantiomers of KDP (**3**). However, the present synthesis



Scheme 4

Reagents and conditions: i, SeO₂ (2 equiv.), HCO₂H (2 equiv.), dioxane, 90 °C, 4 h (68%); ii, LiAlH₄, THF (87%) then *t*-BuMe₂SiCl, Et₃N, CH₂Cl₂, room temp. (89%); iii, MnO₂, benzene-CH₂Cl₂ (1:1), room temp. (81%); iv, *i*-Bu₃AlH, CuI, HMPA-THF (1:4), -78 °C (92%); v, pyrrolidine, benzene, reflux then (TsSCH₂)₂CH₂, Et₃N, MeCN, reflux (85%); vi, *t*-BuOK (1.5 equiv.), *t*-BuOH, trace H₂O, -50 °C, acid workup then CH₂N₂ (60%); vii, MeI, CaCO₃, H₂O-MeCN (1:4), reflux (90%); viii, I₂, KOH, MeOH, -10 °C; ix, HF-pyridine, THF, room temp. (61% from 22).

has more potential value for the stereocontrolled construction of a variety of modified kainoid amino acids for biological investigation based on the functionality of the tricyclic starting material **3** which allows various stereocontrolled modifications⁴ not only on the side chain moieties, but also on the core pyrrolidine framework.

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