Pergamon

Tetrahedron Letters, Vol. 38, No. 5, pp. 857-860, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02467-7

An Enantioconvergent Route to (–)-Kainic Acid

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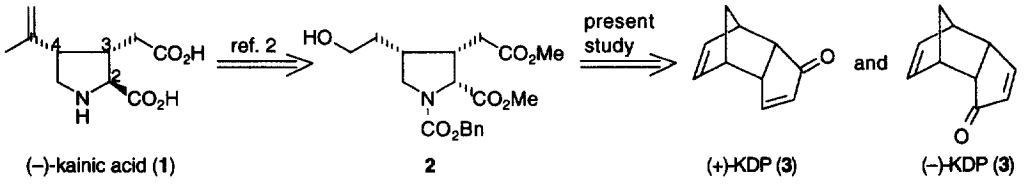
Abstract: A new stereocontrolled route to (–)-kainic acid, the representative of the kainoid amino acids and exhibiting insecticidal, anthelmintic and neuroexcitatory properties, has been devised in an enantioconvergent way using either (+)- or (–)-ketodicyclopentadiene as the starting material by employing a concurrent retro-Diels-Alder reaction and intramolecular ene reaction as the key step.

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] **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**).

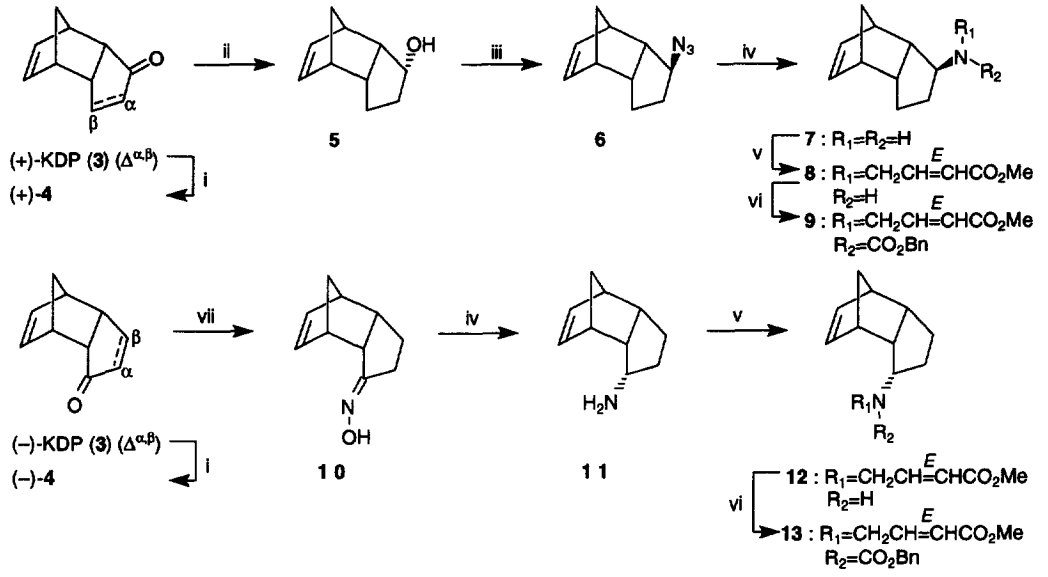


Scheme 1

(+)-KDP [(+)-**3**] (>99% ee) was transformed stereoselectively into the *endo*-alcohol[5] **5**, mp 96 °C, $[\alpha]_D^{28}$ −13.1 (*c* 0.5, $CHCl_3$), in 88% yield *via* the (+)-ketone[6] (+)-**4**. The Mitsunobu reaction[7] of **5** with diphenylphosphoryl azide (DPPA) gave the *exo*-azide **6**, $[\alpha]_D^{27}$ +70.4 (*c* 1.0, $CHCl_3$), with inversion which was sequentially transformed into the *exo*-carbamate **9**, $[\alpha]_D^{25}$ +49.1 (*c* 1.0, $CHCl_3$), 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, $CHCl_3$), *via* the (–)-ketone[6] (–)-**4**. On sequential stereoselective reduction, *N*-alkylation, and carbamoylation, **10** furnished the *endo*-carbamate **13**, $[\alpha]_D^{27}$ –83.8 (*c* 1.6, $CHCl_3$), *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**).



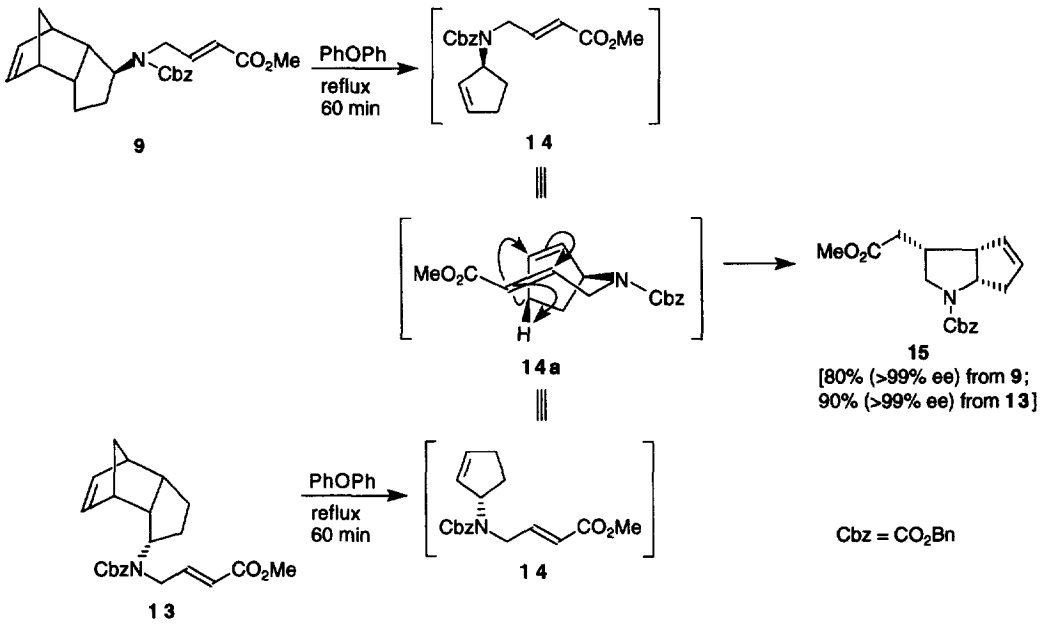
Scheme 2

Reagents and conditions: i, Zn, AcOH-EtOH (1:4), reflux [97% for (–)-**4**]; ii, $NaBH_4$, MeOH, –78 °C [88% from (+)-**3**]; iii, DPPA, ($NCO_2Et)_2$, PPh_3, THF, 0 °C ~ room temp. (94%); iv, $LiAlH_4$, THF, room temp.; v, $BrCH_2CH{=}CHCO_2Me$, Et_3N, DMF, 0 °C; vi, $ClCO_2Bn$, NaH, DMF, –20 °C [47% for **9** from **6** and 49% for **13** from (–)-**3**]; vii, $NH_2OH{\cdot}HCl$, 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 point[8] (~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 reaction[9] 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, $CHCl_3$), 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, $CHCl_3$), 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*-

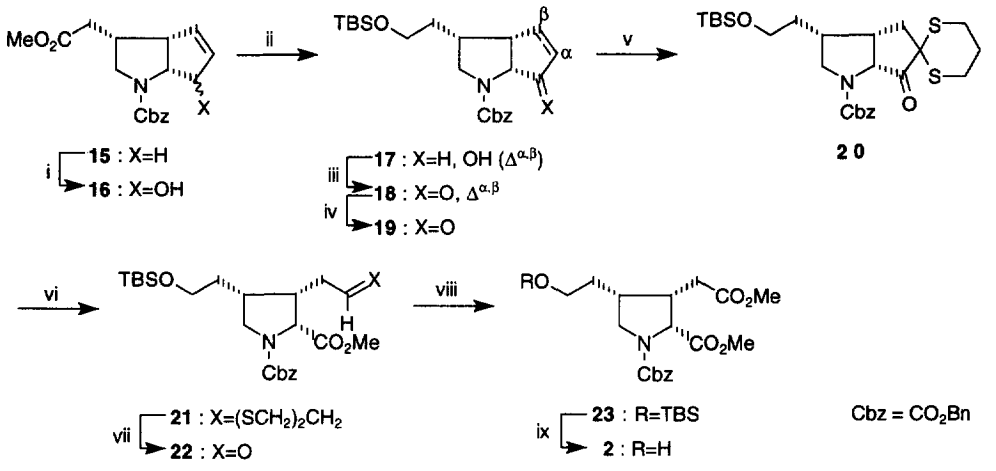
PrOH/hexane), indicating that the original chiral integrity of the precursor carbamates was preserved under these thermal conditions. The relative stereochemistry of **15** was determined to be the all-*cis* configuration as shown by facile iodolactone formation (single product in 73% yield) when the carboxylate generated from **15** by saponification was treated with iodine in acetonitrile[10]; its absolute stereochemistry, however, was determined after converting it into the key intermediate[2] **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 acid[11] 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, $CHCl_3$), in 58% overall yield *via* the silyl ether **17** and the enone **18**, $[\alpha]_D^{27}$ +124.0 (*c* 1.6, $CHCl_3$). The ketone **19** was transformed into the α-diketone monothioketal[13] **20**, $[\alpha]_D^{21}$ –21.8 (*c* 1.1, $CHCl_3$), in 85% yield which was cleaved under basic conditions[13] to give the dithiane **21**, $[\alpha]_D^{28}$ –7.1 (*c* 1.0, $CHCl_3$), in 60% yield after esterification. Hydrolysis of the dithiane group[13] of **21** afforded the aldehyde **22**, $[\alpha]_D^{27}$ +19.2 (*c* 0.7, $CHCl_3$), 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, $CHCl_3$) [lit.[2b]: $[\alpha]_D^{27}$ +11.7 (*c* 0.5, $CHCl_3$)], in 61% yield after desilylation[15] of the resulting monocyclic silyl ether **23**, $[\alpha]_D^{28}$ +32.8 (*c* 0.1, $CHCl_3$) (**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, SeO_2 (2 equiv.), HCO_2H (2 equiv.), dioxane, 90 °C, 4 h (68%); ii, $LiAlH_4$, THF (87%) then *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2, room temp. (89%); iii, MnO_2, benzene-CH_2Cl_2 (1:1), room temp. (81%); iv, *i*-Bu_2AlH, CuI, HMPA-THF (1:4), –78 °C (92%); v, pyrrolidine, benzene, reflux then $(TsSCH_2)_2CH_2$, Et_3N, MeCN, reflux (85%); vi, *t*-BuOK (1.5 equiv.), *t*-BuOH, trace H_2O, ~50 °C, acid workup then CH_2N_2 (60%); vii, MeI, $CaCO_3$, H_2O-MeCN (1:4), reflux (90%); viii, I_2, 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 modifications[4] not only on the side chain moieties, but also on the core pyrrolidine framework.

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(*Received in Japan* 21 *November* 1996; *revised* 12 *December* 1996; *accepted* 16 *December* 1996)