A NEW ENANTIOCONTROLLED ROUTE TO (–)-KAINIC ACID†

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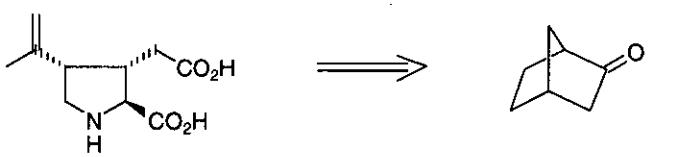
Abstract —— A new route to (–)-kainic acid, the parent member of the kainoids, has been developed using (+)-norcamphor as the starting material.

(–)-Kainic acid (**1**), isolated from the marine alga *Digenea simplex*, is the parent member of the kainoids displaying potent anthelmintic and neuroexcitatory properties.[1] Because of its biological importance as well as its synthetic interest furnishing two additional functionalities on the (*S*)-proline framework, nine enantiocontrolled syntheses have been disclosed so far by employing a variety of methodologies.[2,3] We report here a new procedure for the construction of (–)-kainic acid (**1**) starting from (+)-norcamphor[4,5] (**2**) by connection between N1 and C2 of the target molecule in the key stage of the synthesis (**Scheme 1**).

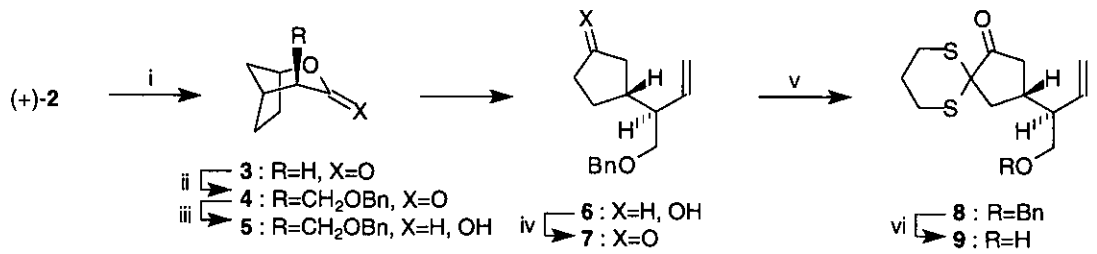


(–)-kainic acid (**1**) (+)-norcamphor (**2**)

Scheme 1

We have already reported[5a] an efficient transformation of (+)-norcamphor (**2**) into the optically pure α-diketone monothioketal derivative (**9**) by the sequence of the reactions involving (i) Baeyer-Villiger oxidation [(+)-**2** → **3**], (ii) stereoselective *exo*-alkylation (**3** → **4**), (iii) Wittig olefination (**4** → **6**), and (iv) regioselective α-dithioketalization (**7** → **8**) (**Scheme 2**). The compound (**9**) containing three chemically distinguishable carbonyl functionalities has been shown to be useful in particular for the stereocontrolled construction of the monoterpenes and the indole alkaloids biogenetically originated from secologanin.[5a]

† Dedicated to Prof. Sigeru Oae on the occasion of his 77th birthday.

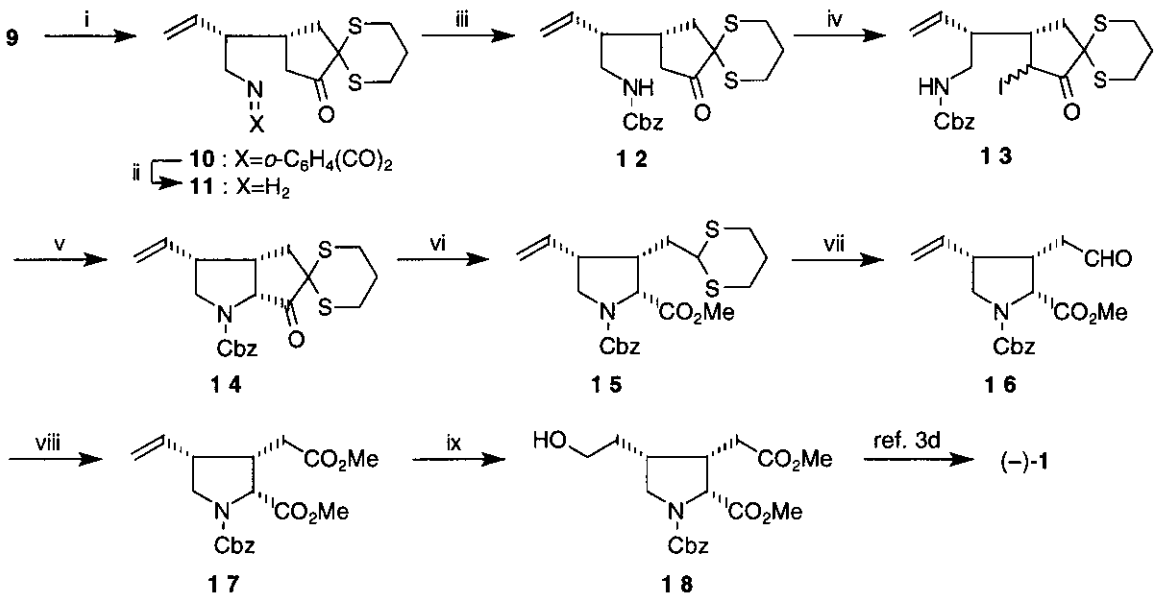


Scheme 2

Reagents and conditions: i) mCPBA, CH_2Cl_2, 88%; ii) $BnOCH_2I$ (1.5 equiv.), LDA (1.3 equiv.), THF, –78 °C, 52% (78% based on consumed **3**); iii) DIBAL, CH_2Cl_2, –78 °C, then $Ph_3P{=}CH_2$, 68%; iv) PCC, NaOAc, CH_2Cl_2, 100%; v) pyrrolidine, benzene, reflux, then $CH_2(CH_2STs)_2$, Et_3N, MeCN, 70%; vi) BBr_3, CH_2Cl_2, –78 °C, 82%.

We report here another utility of the compound (**9**) as the starting material of (–)-kainic acid (**1**).

To obtain (–)-kainic acid (**1**), the primary alcohol (**9**) (>99% ee)[7] was subjected to the Mitsunobu reaction[8] to give the phthalimide (**10**), mp 168-171 °C, $[\alpha]_D^{27}$ –67.5° (*c* 1.0, $CHCl_3$), in 98% yield. The imide (**10**), on treatment with methanolic methylamine[9] followed by carbamoylation of the resulting primary amine (**11**) with carbobenzoxy chloride, furnished the carbamate (**12**), $[\alpha]_D^{28}$ –58.1° (*c* 1.0, $CHCl_3$), in 71% yield. In order to construct the requisite pyrrolidine framework, **12** was first exposed to iodine in the presence of lithium diisopropylamide (LDA) to yield the α-iodoketone (**13**) which without purification was next treated with potassium *tert*-butoxide to give the cyclization product (**14**), $[\alpha]_D^{25}$ –44.4° (*c* 1.7, $CHCl_3$), in 68% yield as a single product by formation of the nitrogen-carbon bond. Cleavage of the α-diketone monothioketal functionality of **14** was readily carried out with potassium hydroxide in warm *tert*-butyl alcohol[6,10] to give the dithiane-ester (**15**), $[\alpha]_D^{29}$ –29.6° (*c* 1.4, $CHCl_3$), in 50% yield after treatment with diazomethane. However, hydrolysis of **15** was accompanied by an intractable mixture resulted by the interaction between proximal vinyl and dithiane functionalities under the conditions which diminished the overall yield of the desired diester (**17**), $[\alpha]_D^{27}$ –5.3° (*c* 0.3, $CHCl_3$), to 32% after oxidative esterification of the resulting aldehyde (**16**) with iodine in alkaline methanol.[11] Finally, **17** was treated under standard hydroboration-oxidation conditions to afford the known primary alcohol (**18**), $[\alpha]_D^{27}$ +11.7° (*c* 0.5, $CHCl_3$), in 74% yield. Since the all *cis*-trisubstituted pyrrolidine (**18**) has been transformed[3d] into (–)-kainic acid (**1**) without difficulty, the present transformation constitutes a formal synthesis of this natural product (**Scheme 3**).



Scheme 3

Reagents and conditions: i) phthalimide, DEAD, PPh_3, THF, 98%; ii) $MeNH_2$, MeOH, reflux; iii) $ClCO_2Bn$, Et_3N, CH_2Cl_2, 0 °C, 71% from **10**; iv) LDA, I_2, THF, –78 °C; v) *tert*-BuOK, DMF, 0 °C, 68% from **12**; vi) KOH, *tert*-BuOH, 50 °C, then 1 N HCl, CH_2N_2, 50%; vii) MeI, $CaCO_3$, aq. MeCN, 80 °C, overnight, 45%; viii) I_2, KOH, MeOH, room temp, 70%; ix) $BH_3 \cdot Me_2S$, THF, 0 °C, then 5% $NaHCO_3$, 30% H_2O_2, room temp, 74%.

In summary, although the present synthesis necessitates some improvements from the practical point of view, we have demonstrated the first instance constructing the pyrrolidine ring of the kainoid by the N1-C2 connection.

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7. Optically pure material was obtained after recrystallization, mp 81.0 - 81.5 °C, $[\alpha]_D^{32}$ +109.0° (*c* 1.7, $CHCl_3$) (>99% ee, CHIRALCEL OD, 10% *i*-PrOH-hexane).

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