

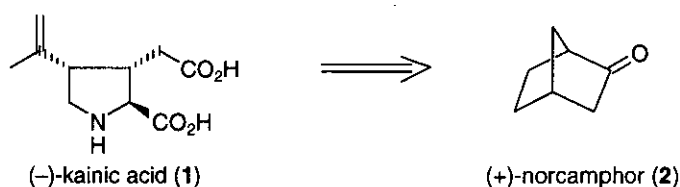
A NEW ENANTIOCONTROLLED ROUTE TO (-)-KAINIC ACID<sup>†</sup>

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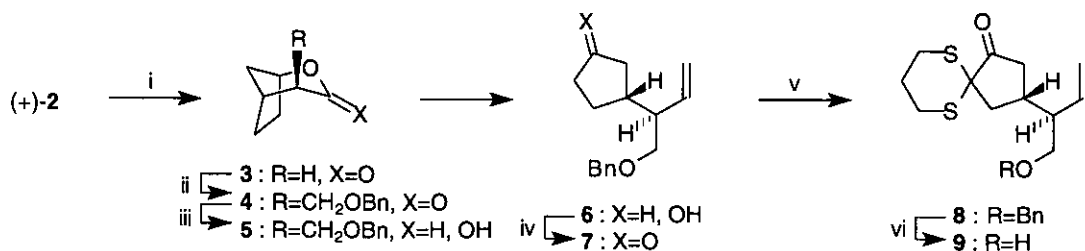
*Abstract* — A new route to (-)-kainic acid, the parent member of the kainoids, has been developed using (+)-norcamphor as the starting material.

(-)-Kainic acid (**1**), isolated from the marine alga *Digenea simplex*, is the parent member of the kainoids displaying potent anthelmintic and neuroexcitatory properties.<sup>1</sup> 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.<sup>2,3</sup> We report here a new procedure for the construction of (-)-kainic acid (**1**) starting from (+)-norcamphor<sup>4,5</sup> (**2**) by connection between N1 and C2 of the target molecule in the key stage of the synthesis (**Scheme 1**).

**Scheme 1**

We have already reported<sup>5a</sup> an efficient transformation of (+)-norcamphor (**2**) into the optically pure  $\alpha$ -diketone monothioketal derivative (**9**) by the sequence of the reactions involving (i) Baeyer-Villiger oxidation [(+)-**2**  $\rightarrow$  **3**], (ii) stereoselective *exo*-alkylation (**3**  $\rightarrow$  **4**), (iii) Wittig olefination (**4**  $\rightarrow$  **6**), and (iv) regioselective  $\alpha$ -dithioketalization (**7**  $\rightarrow$  **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.<sup>5a</sup>

<sup>†</sup> Dedicated to Prof. Sigeru Oae on the occasion of his 77th birthday.

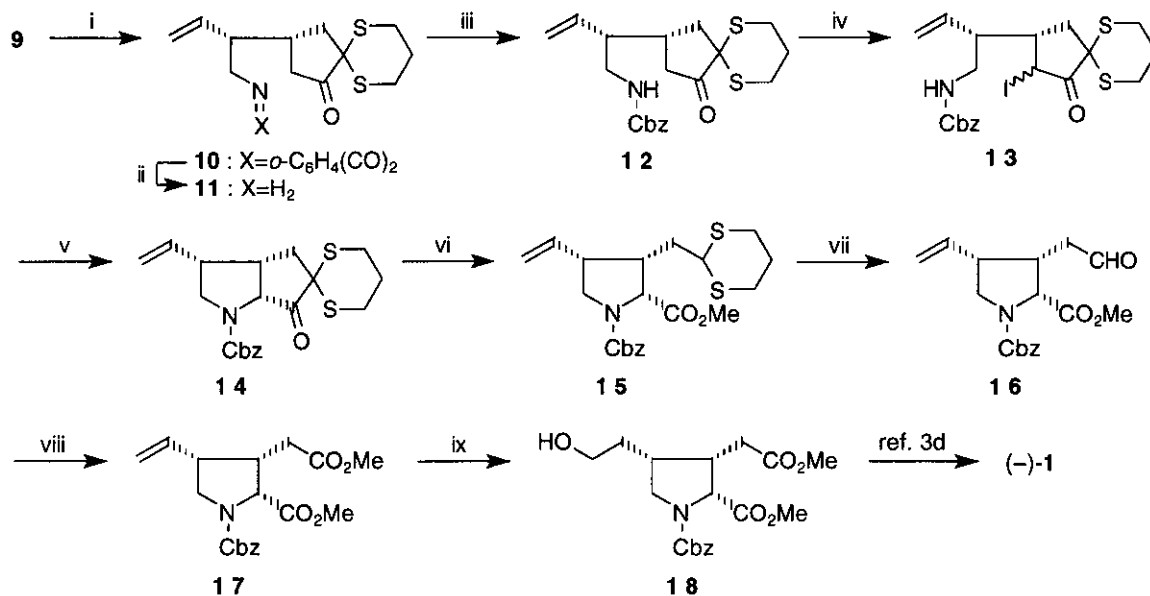


Scheme 2

**Reagents and conditions:** i) mCPBA,  $CH_2Cl_2$ , 88%; ii)  $BnOCH_2I$  (1.5 equiv.), LDA (1.3 equiv.), THF,  $-78^\circ C$ , 52% (78% based on consumed **3**); iii) DIBAL,  $CH_2Cl_2$ ,  $-78^\circ C$ , 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)  $BBr_3$ ,  $CH_2Cl_2$ ,  $-78^\circ C$ , 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)<sup>7</sup> was subjected to the Mitsunobu reaction<sup>8</sup> to give the phthalimide (**10**), mp 168–171  $^\circ C$ ,  $[\alpha]_D^{27} -67.5^\circ$  (*c* 1.0,  $CHCl_3$ ), in 98% yield. The imide (**10**), on treatment with methanolic methylamine<sup>9</sup> followed by carbamoylation of the resulting primary amine (**11**) with carbobenzoxy chloride, furnished the carbamate (**12**),  $[\alpha]_D^{28} -58.1^\circ$  (*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  $\alpha$ -iodoketone (**13**) which without purification was next treated with potassium *tert*-butoxide to give the cyclization product (**14**),  $[\alpha]_D^{25} -44.4^\circ$  (*c* 1.7,  $CHCl_3$ ), in 68% yield as a single product by formation of the nitrogen-carbon bond. Cleavage of the  $\alpha$ -diketone monothioetal functionality of **14** was readily carried out with potassium hydroxide in warm *tert*-butyl alcohol<sup>6,10</sup> to give the dithiane-ester (**15**),  $[\alpha]_D^{29} -29.6^\circ$  (*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**),  $[\alpha]_D^{27} -5.3^\circ$  (*c* 0.3,  $CHCl_3$ ), to 32% after oxidative esterification of the resulting aldehyde (**16**) with iodine in alkaline methanol.<sup>11</sup> Finally, **17** was treated under standard hydroboration-oxidation conditions to afford the known primary alcohol (**18**),  $[\alpha]_D^{27} +11.7^\circ$  (*c* 0.5,  $CHCl_3$ ), in 74% yield. Since the all *cis*-trisubstituted pyrrolidine (**18**) has been transformed<sup>3d</sup> 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,  $\text{PPh}_3$ , THF, 98%; ii)  $\text{MeNH}_2$ , MeOH, reflux; iii)  $\text{ClCO}_2\text{Bn}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 71% from 10; iv) LDA,  $\text{I}_2$ , THF, -78 °C; v)  $\text{tert-BuOK}$ , DMF, 0 °C, 68% from 12; vi) KOH, *tert-BuOH*, 50 °C, then 1 N HCl,  $\text{CH}_2\text{N}_2$ , 50%; vii) MeI,  $\text{CaCO}_3$ , aq. MeCN, 80 °C, overnight, 45%; viii)  $\text{I}_2$ , KOH, MeOH, room temp, 70%; ix)  $\text{BH}_3 \cdot \text{Me}_2\text{S}$ , THF, 0 °C, then 5%  $\text{NaHCO}_3$ , 30%  $\text{H}_2\text{O}_2$ , 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.

## ACKNOWLEDGEMENTS

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