A New Enantiospecific Route to (−)-Kainic Acid *via* the Intramolecular Pauson–Khand Reaction

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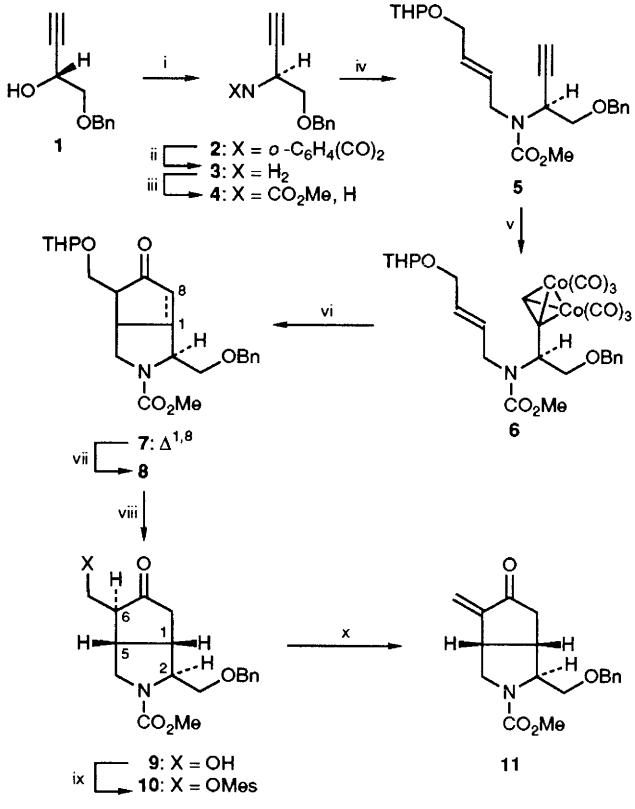
A new enantiospecific route to (−)-kainic acid is established starting with (*R*)-4-benzyloxy-1-butyn-3-ol by employing the intramolecular Pauson–Khand reaction as the key step.

Recently, we developed an efficient enantiocontrolled method for the synthesis of optically active 3-hydroxyacetylenes from allylic alcohols.[1] Starting with (*R*)-4-benzyloxy-1-butyn-3-ol[1,2] **1** obtained by this method, we have now established a new enantiospecific synthesis of natural (−)-kainic acid[3,4] **20**, the parent member of the kainoids known by anthelmintic and neuro-excitatory activities, by employing the intramolecular Pauson–Khand reaction[5] as the key step.

The acetylene alcohol **1** was first transformed into the primary amine† **3**, $[\alpha]_D^{31}$ +8.1° (*c* 1.29, $CHCl_3$), with inversion of chirality[6] *via* the phthalimide‡ **2**, $[\alpha]_D^{30}$ + 34.2° (*c* 0.82, $CHCl_3$), in 95% overall yield. Compound **3** was then converted into the tertiary carbamate§ **5**, $[\alpha]_D^{27}$ + 11.2° (*c* 1.33, $CHCl_3$), in 80% overall yield *via* **4**, $[\alpha]_D^{28}$ + 33.3° (*c* 2.08, $CHCl_3$), by sequential carbamoylation and alkylation. Treatment of **5** with dicobalt octacarbonyl furnished the complex **6**, in 82% yield, which on treatment with an excess of *N*-methylmorphorine *N*-oxide[7] (NMO) afforded an inseparable mixture of the bicyclic enones **7** in 85% yield. The mixture was reduced with a complex[8] prepared from lithium aluminium hydride and copper(I) iodide in a mixture of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) to give an inseparable mixture of the saturated bicyclic ketones **8**, which on removal of the THP group with acidic methanol, furnished the *trans*-1,2 : *cis*-1,5 : *trans*-5,6-adduct **9**, $[\alpha]_D^{30}$–18.3° (*c* 0.62, $CHCl_3$), in 60% yield after separation of the isomeric *cis*-1,2 : *cis*-1,5 : *trans*-5,6-adduct, $[\alpha]_D^{30}$ −39.7° (*c* 0.70, $CHCl_3$), in 10% yield, by silica gel column chromatography. The alcohol **9** was then treated sequentially with methanesulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the enone **11** in 80% yield *via* the methanesulfonate **10** (Scheme 1).

The enone **11**, on treatment with a complex[8] prepared from diisobutylaluminium hydride (DIBAL) and copper(I) iodide in a mixture of THF and HMPA, followed by an excess of paraformaldehyde in the same flask, furnished the ketol **13**, $[\alpha]_D^{30}$ +18.2° (*c* 1.91, $CHCl_3$), as a single epimer in 85% yield by stereospecific reaction from the convex face of the transient enolate **12**. Baeyer–Villiger reaction of **13** proceeded in a regioselective way to give the δ-lactone **14**, $[\alpha]_D^{28}$ −12.2° (*c* 2.03, $CHCl_3$), in 68% yield (89% based on recovered **13**) as a single oxidation product. On exposure to iodine and

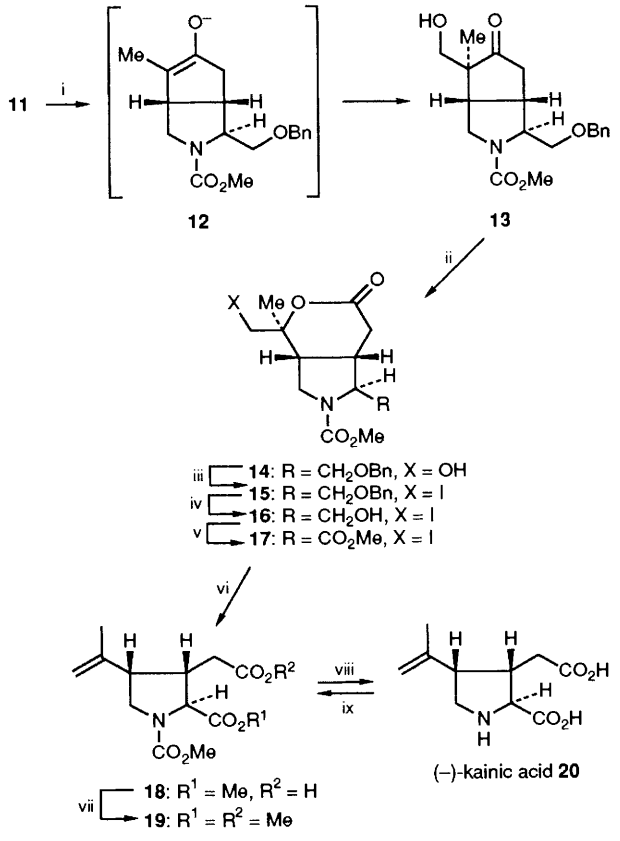


Scheme 1 *Reagents and conditions*: i, phthalimide, $Pr^iO_2CN{=}NCO_2Pr^i$, Ph_3P, THF, room temperature; ii, $H_2NNH_2{\cdot}H_2O$, EtOH, reflux; iii, $ClCO_2Me$, Et_3N, CH_2Cl_2, 0 °C ~ room temp.; iv, (*E*)-$THPOCH_2CH{=}CHCH_2Cl$, NaH, DMF, 0 °C ~ room temp.; v, $Co_2(CO)_8$ (1.2 equiv.), benzene, room temp.; vi, NMO (6 equiv.), CH_2Cl_2, 0 °C; vii, $LiAlH_4$, CuI, HMPA–THF (1 : 4), −78 °C; viii, toluene-*p*-sulfonic acid, MeOH, room temp., then separation by SiO_2 column; ix, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; x, DBU, CH_2Cl_2, room temp. Bn = benzyl

† All new compounds gave the expected analytical (combustion and/or high resolution mass) and spectral (IR, NMR and mass) data.

‡ Optical purity of **2** was determined to be >98% e.e. by ^1H NMR (500 MHz) spectra of the α-methoxy-α-trifluoromethylphenylacetate (MTPA) [(*R*)- and (*S*)-] esters of the debenzylated product.

§ A diastereoisomeric mixture at O–THP bond.



Scheme 2 *Reagents and conditions*: i, DIBAL, CuI, HMPA–THF (1:4), −78 °C, then $(HCHO)_n$, −78 °C ~ room temp.; ii, *m*-CPBA (5 equiv.), $NaHCO_3$, CH_2Cl_2, room temp.; iii, I_2, PPh_3, imidazole, THF–MeCN (4:1), reflux; iv, BBr_3, CH_2Cl_2, −50 °C; v, Jones oxidation, 0 °C ~ room temp., then MeI, K_2CO_3, DMF, 0 °C ~ room temp.; vi, Zn, AcOH (cat.), EtOH, ultrasound, room temp.; vii, MeI, K_2CO_3, DMF, room temp.; viii, 40% aq. NaOH–MeOH (1:1), reflux; ix, $ClCO_2Me$, Pr^i_2NEt, DMF, 0 °C ~ room temp., then MeI, K_2CO_3, DMF, 0 °C ~ room temp.

triphenylphosphine[9] **14** gave the iodide **15**, $[\alpha]_D^{32}$ −30.1° (*c* 0.42, $CHCl_3$), which was then transformed into the lactone ester **17**, $[\alpha]_D^{30}$ +9.0° (*c* 0.52, $CHCl_3$), by sequential debenzylation, Jones oxidation and methylation. Overall yield of **17** from **14** was 35%.

Treatment of **17** with zinc powder under sonication brought about facile reductive cleavage to give the trisubstituted pyrrolidine **19**, $[\alpha]_D^{30}$ −25.6° (*c* 0.86, $CHCl_3$), having the functionalities with the requisite oxidation stage and the stereochemistry in 59% yield after esterification of the resulting acid **18**. The structure of **19** was confirmed by comparison with an authentic material, $[\alpha]_D^{29}$ −23.8° (*c* 1.07, $CHCl_3$), prepared from (−)-kainic acid **20** in sequential carbamoylation and esterification (51% overall). Finally, **19** was hydrolysed by refluxing methanolic aqueous sodium hydroxide[4d] (1:1) to afford (−)-kainic acid **20**, m.p. 237–245 °C (decomp.), $[\alpha]_D^{30}$ −13.9° (*c* 0.50, H_2O), in 70% yield, which was identical with an authentic material,[4d] m.p. 243–244 °C (decomp.), $[\alpha]_D^{22}$ −14.2° (*c* 0.23, H_2O), in all respects.

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