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 reaction⁵ as the key step.

The acetylene alcohol 1 was first transformed into the primary amine[†] **3**, $[\alpha]_D{}^{31}$ +8.1° (*c* 1.29, CHCl₃), with inversion of chirality⁶ via the phthalimide[‡] **2**, $[\alpha]_D{}^{30}$ + 34.2° (c 0.82, CHCl₃), in 95% overall yield. Compound 3 was then converted into the tertiary carbamate§ 5, $[\alpha]_D^{27}$ + 11.2° (c 1.33, CHCl₃), 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-oxide7 (NMO) afforded an inseparable mixture of the bicyclic enones 7 in 85% yield. The mixture was reduced with a complex⁸ prepared from lithium aluminium hydride and copper(1) 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-5,6adduct 9, $[\alpha]_{D}^{30}$ -18.3° (c 0.62, CHCl₃), in 60% yield after separation of the isomeric cis-1,2: cis-1,5: trans-5,6-adduct, $[\alpha]_{D}^{30} - 39.7^{\circ}$ (c 0.70, CHCl₃), 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 complex⁸ prepared from diisobutylaluminium hydride (DIBAL) and copper(1) iodide in a mixture of THF and HMPA, followed by an excess of paraformaldehyde in the same flask, furnished the ketol 13, $[\alpha]_D^{30} + 18.2^{\circ}$ (*c* 1.91, CHCl₃), 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, $[\alpha]_D^{28} - 12.2^\circ$ (*c* 2.03, CHCl₃), in 68% yield (89% based on recovered 13) as a single oxidation product. On exposure to iodine and

THPC

OBr ÒBn ÒBn 2: X = *o* -C₆H₄(CO)₂ 3: X = H₂ 4: X = CO₂Me, H ĊO₂Me 5 THPC THPO Co(CO)₃ ,Co(CO)3 vi ,H OBn OBn ĊO₂Me ĊO₂Me 6 7: ∆^{1,8} OBn OBn ĊO₂Me ĊO₂Me 9: X = OH 11 10: X = OMes

Scheme 1 Reagents and conditions: i, phthalimide, $PriO_2CN=NCO_2Pri$, Ph_3P , THF, room temperature; ii, $H_2NNH_2 \cdot H_2O$, EtOH, reflux; iii, $CICO_2Me$, Et_3N , CH_2Cl_2 , $0 \ ^{\circ}C \ \sim$ room temp.; iv, (*E*)-THPOCH₂CH=CHCH₂Cl, NaH, DMF, $0 \ ^{\circ}C \ \sim$ room temp.; v, $Co_2(CO)_8$ (1.2 equiv.), benzene, room temp.; vi, NMO (6 equiv.), CH_2Cl_2 , $0 \ ^{\circ}C$; vii, LiAlH₄, CuI, HMPA–THF (1:4), $-78 \ ^{\circ}C$; vii, toluene-*p*-sulfonic acid, MeOH, room temp., then separation by SiO₂ column; ix, MeSO₂Cl, Et_3N , CH_2Cl_2 , $0 \ ^{\circ}C$; 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.), NaHCO₃, CH₂Cl₂, room temp.; iii, I₂, PPh₃, imidazole, THF-MeCN (4:1), reflux; iv, BBr₃, CH₂Cl₂, -50 °C; v, Jones oxidation, 0 °C ~ room temp.; then MeI, K₂CO₃, DMF, 0 °C ~ room temp.; vi, Zn, AcOH (cat.), EtOH, ultrasound, room temp.; vii, MeI, K₂CO₃, DMF, room temp.; viii, 40% aq. NaOH-MeOH (1:1), reflux; ix, CICO₂Me, Pri₂NEt, DMF, 0 °C ~ room temp.; then MeI, K₂CO₃, DMF, 0 °C ~ room temp.

triphenylphosphine⁹ **14** gave the iodide **15**, $[\alpha]_D{}^{32}-30.1^\circ$ (*c* 0.42, CHCl₃), which was then transformed into the lactone ester **17**, $[\alpha]_D{}^{30} + 9.0^\circ$ (*c* 0.52, CHCl₃), 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**, $[\alpha]_D^{30} - 25.6^\circ$ (*c* 0.86, CHCl₃), having the

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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, $[\alpha]_D^{29} - 23.8^{\circ}$ (*c* 1.07, CHCl₃), 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.), $[\alpha]_D^{30} - 13.9^{\circ}$ (*c* 0.50, H₂O), in 70% yield, which was identical with an authentic material,^{4d} m.p. 243-244 °C (decomp.), $[\alpha]_D^{22} - 14.2^{\circ}$ (*c* 0.23, H₂O), in all respects.

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