A Concise Enantioselective Route to (−)-Kainic acid from (*S*)-2-(Benzyloxymethyl)oxirane

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A concise enantioselective route to (−)-kainic acid (**1**) from (*S*)-2-(benzyloxymethyl)oxirane (**2**) has been established by enantio- and diastereo-selective intramolecular 1,3-dipolar cyclization.

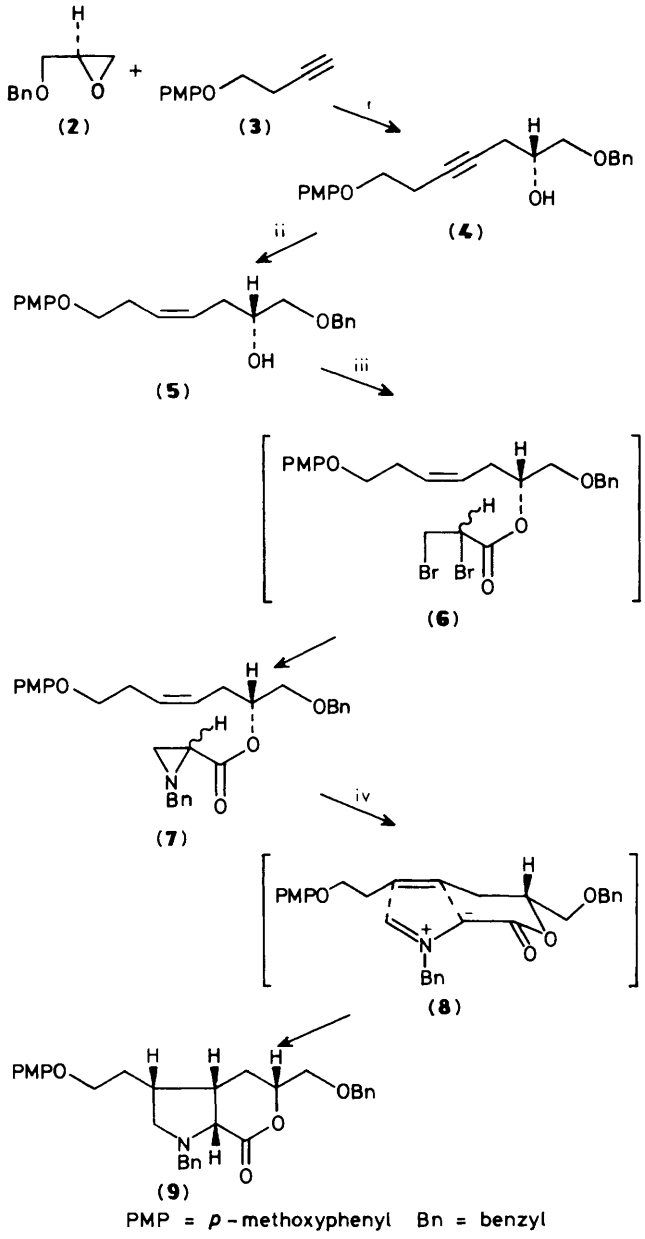
(−)-Kainic acid (**1**),[1] the parent of the kainoid amino acids, has attracted considerable interest owing to its neuroexcitant properties[2] as well as its anthelmintic and insecticidal activities.[3] Herein, we report a concise route to (−)-kainic acid (**1**)[4] from (*S*)-2-(benzyloxymethyl)oxirane (**2**), employing the recently developed enantio- and diastereo-selective intramolecular 1,3-dipolar cyclization[5] as the key step. This allows the construction of three chiral centres with complete selectivity in a single stage.

Reaction of the oxirane (**2**)[6] with the lithium acetylide generated from but-3-ynyl *p*-methoxyphenyl ether (**3**)†‡ with methyl-lithium in ether gave the secondary alcohol (**4**), $[\alpha]_D^{26}$ −9.3° (*c* 1.03, $CHCl_3$), in 74% yield. Partial reduction of (**4**) gave the *Z*-olefin (**5**), $[\alpha]_D^{26}$ +7.8° (*c* 1.1, $CHCl_3$), in 95% yield, which on sequential treatment with 2,3-dibromopropionyl chloride in methylene chloride in the presence of triethylamine followed by benzylamine in the same reaction medium[7] afforded the aziridine ester (**7**) in 98% yield as a mixture (1 : 1) of diastereoisomers [*via* (**6**)].

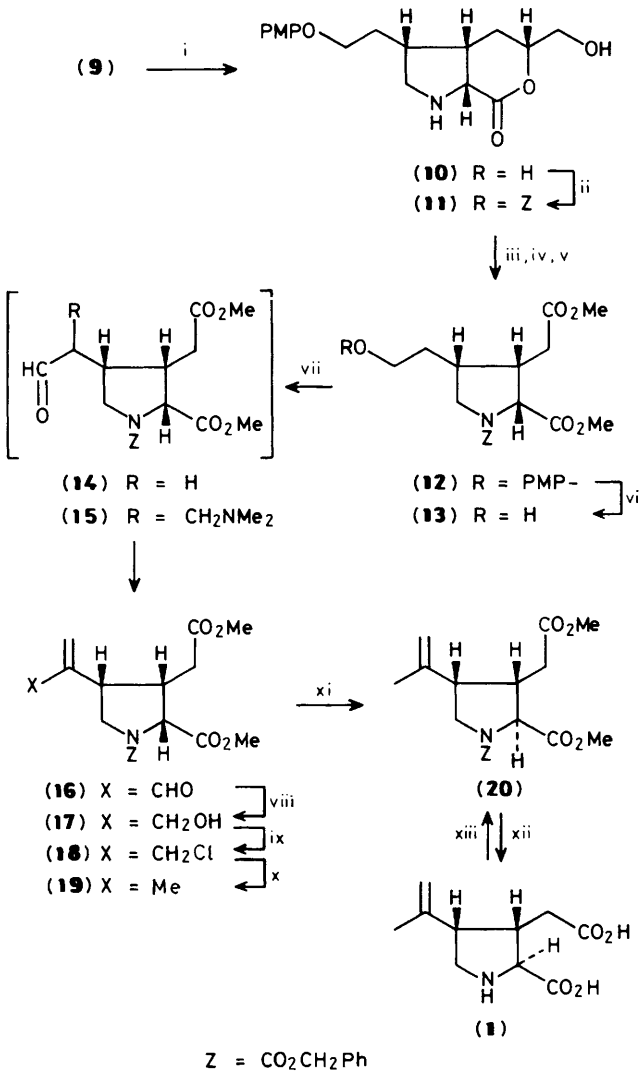
Thermolysis of (**7**) in xylene (1.25% solution) at 305—310 °C for 5 min (glass-sealed tube) allowed concomitant azomethine ylide (**8**) formation and diastereoselective intramolecular cycloaddition to give the pyrrolidine lactone (**9**) in 70% yield as a single product. Although the stereochemistry of (**9**) could not be determined at this stage, the following transformations readily revealed that the product (**9**) possessed the all-*cis* configuration shown. The observed stereochemical outcome may be explained by assuming the *exo*-conformation (**8**) for the active intermediate in which the bulky benzyloxymethyl group assumes an equatorial orientation with respect to the forming δ-lactone moiety. Catalytic bisdebenzylation of (**9**) followed by treatment of the resulting secondary amino alcohol (**10**) with benzyl chloroformate in the presence of triethylamine gave the carbamate (**11**) in 72% overall yield. Hydrolysis of the lactone moiety of (**11**) followed by sequential oxidative treatment[8] (CrO_3 and HIO_4) and esterification with diazomethane furnished the dimethyl ester (**12**), $[\alpha]_D^{24}$ +10.4° (*c* 1.04, $CHCl_3$), in 52% overall yield. Treatment of (**12**) with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile (20%) allowed smooth ether cleavage[9] to give the primary alcohol (**13**) in 88% yield. Oxidation of

† Compound (**3**) was prepared in 82% yield from but-3-yn-1-ol and *p*-methoxyphenol by employing Mitsunobu's conditions, *cf.* O. Mitsunotu, *Synthesis*, 1981, 1.

‡ Satisfactory spectral [i.r., ^{1}H n.m.r. (90 and/or 500 MHz), and mass] and analytical (combustion and/or high resolution mass spectrometric) data were obtained for all new compounds isolated.



Scheme 1. *Reagents and conditions*: i, MeLi, THF, −30 °C to room temp.; ii, H_2/Pd–$CaCO_3$, benzene, iii, 2,3-dibromopropionyl chloride (1.2 equiv.), Et_3N (4 equiv.), CH_2Cl_2, then $BnNH_2$ (3 equiv.), CH_2Cl_2, 0 °C (1 h) to room temp. (1.5 h); iv, 1.25% in xylene, 305—310 °C, 5 min, sealed tube.



Scheme 2. *Reagents and conditions*: i, H_2/$Pd(OH)_2$, HCl (cat.), MeOH; ii, benzyl chloroformate, Et_3N, CH_2Cl_2; iii, NaOH (1.2 equiv.), H_2O–THF (1:2) then CO_2; iv, CrO_3 (4.8 equiv.), HIO_4 (9.6 equiv.); v, CH_2N_2, vi, CAN (2.4 equiv.), MeCN–H_2O (4:1), 0 °C, 0.5 h; vii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −60 °C to room temp., then Eschenmoser's salt (10 equiv.), 20 h; viii, $NaBH_4$ (0.5 equiv.), $CeCl_3$ (1.0 equiv.), MeOH, 0 °C; ix, TsCl (1.1 equiv.), DMAP (cat.), Et_3N, room temp,; x, Bu_3SnH (1.1 equiv.), AIBN (cat.), benzene, reflux, 3 h; xi, NaH (2.5 equiv.), DBU (5 equiv.), benzene, room temp., 24 h; xii, 10 M NaOH, heat; xiii, benzyl chloroformate then CH_2N_2.

(**13**) under Swern's conditions[10] followed by treatment of the reaction mixture containing the aldehyde (**14**) with an excess of methylenedimethylaminoammonium chloride (Eschenmoser's salt) afforded the α,β-unsaturated aldehyde (**16**) in 62% yield [*via* (**15**)] by concurrent Mannich reaction and β-elimination.

Reduction of (**16**) ($NaBH_4$/$CeCl_3$)[11] gave the allyl alcohol (**17**), in 97% yield, which was converted into the chloride (**18**), $[\alpha]_D$ + 18.3° (*c* 1.18, $CHCl_3$), in 67% yield, on treatment with toluene-*p*-sulphonyl chloride in methylene chloride containing triethylamine and 4-dimethylaminopyridine (DMAP).[12] Dechlorination was cleanly carried out by using tri-n-butyltin hydride in the presence of azobisisobutyronitrile (AIBN)[13] to give the 3-isopropenylpyrrolidine (**19**),§ $[\alpha]_D^{24}$ + 19.25° (*c* 0.8, $CHCl_3$), in 80% yield. Although epimerization at the C-3 centre could not be carried out efficiently under conventional conditions, treatment of (**19**) with sodium hydride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene[5] brought about complete inversion to afford the epimer (**20**),§ $[\alpha]_D^{26}$ −22.5° (*c* 1.03, $CHCl_3$), with the requisite configuration, identical with authentic material, $[\alpha]_D^{26}$ −23.0°

§ The ^1H n.m.r. spectra showed the characteristic methine proton signals at δ 4.46 (dd, *J* 6.4 and 2.7 Hz) for (**19**) and at 4.24 (dd, *J* 4.2 and 2.9 Hz) for (**20**).

(*c* 1.0, $CHCl_3$), prepared from natural (−)-kainic acid (**1**). conversion of (**20**) into (−)-kainic acid (**1**) was accomplished on brief heating with aqueous sodium hydroxide.[14]

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