An Enantiospecific Total Synthesis of (−)-α-Kainic Acid

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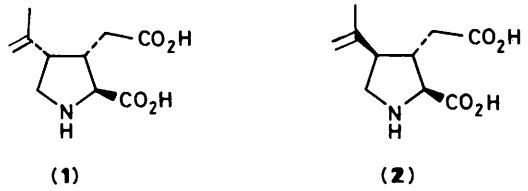
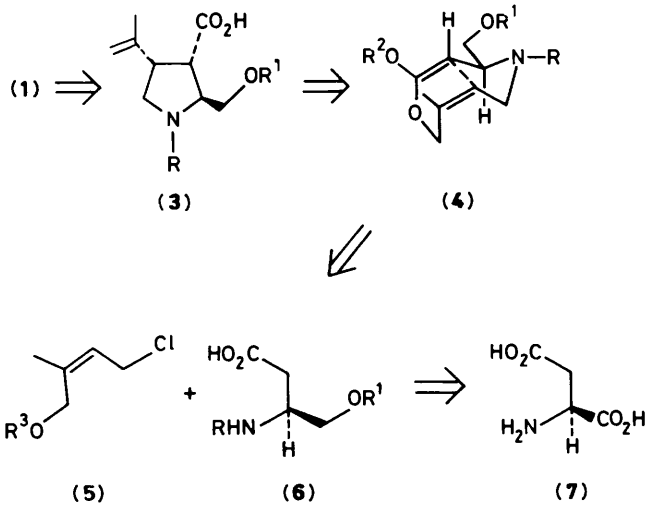
An enantiospecific synthesis of (−)-α-kainic acid (**1**) from L-aspartic acid (**7**) has been achieved in which the C-3 to C-4 bond is formed by a stereocontrolled enolate Claisen rearrangement [(**13**) → (**14**)] which delivers the correct geometry at the C-3 and C-4 asymmetric centres.

(−)-α-Kainic acid (**1**) is the parent member of the kainoids, a unique group of pyrrolidine dicarboxylic acids which have attracted considerable interest principally owing to their pronounced neuroexcitant properties,[1] although anthelmintic and insecticidal activities have also been attributed to members of the group.[2] Kainic acid (**1**)[2a] co-occurs with its C-4 epimer, (+)-α-allokainic acid (**2**),[3] in the marine alga *Digenea simplex* Ag. and has also been found in the alga *Centrocerus clavulatum*.[4] A number of homologues of kainic acid have been discovered, all of which possess the same absolute configuration as acid (**1**) and which differ only in the nature of the side chain at C-4. (−)-Domoic acid[5] has an

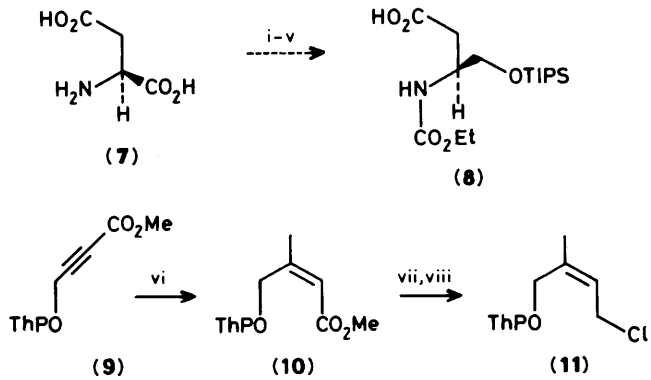


(1) (2)

Scheme 1



(3) (4) (5) (6) (7)



(7) (8) (9) (10) (11)

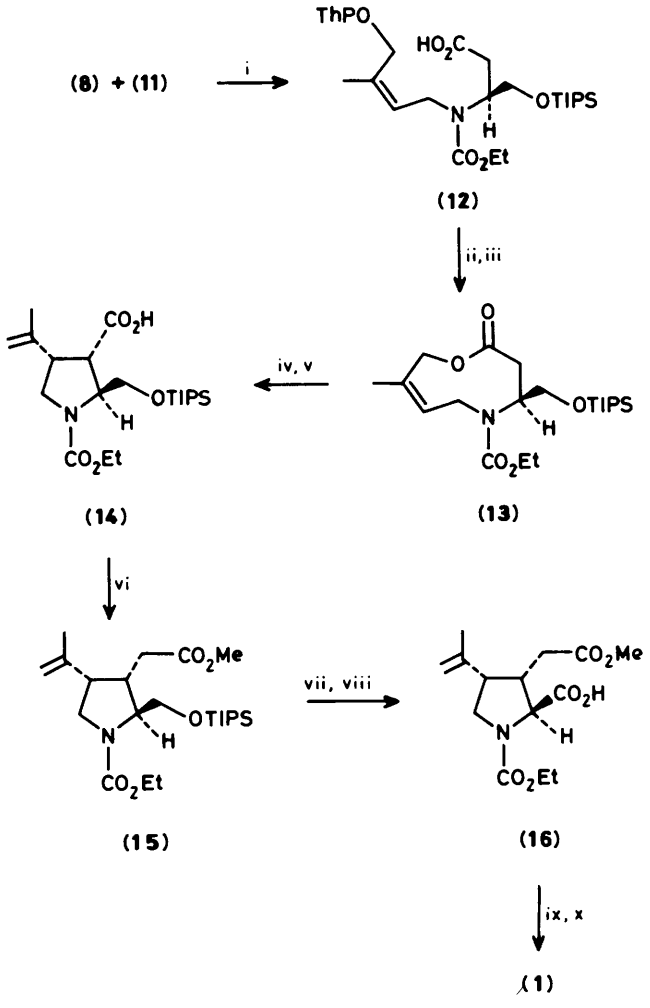
ThP = tetrahydropyranyl

Scheme 2. *Reagents*: i, $SOCl_2$, MeOH (62%); ii, $ClCO_2Et$ (95%); iii, BH_3·THF (tetrahydrofuran), 0 °C, 16 h (42%); iv, TIPSCl, imidazole, dimethylformamide (DMF), 20 °C, 20 h (95%); v, KOH, MeOH–H_2O, 20 °C, 20 h (75%); vi, Me_2CuLi, THF, −78 °C (90%); vii, Bu^i_2AlH, Et_2O, −70 °C (90%); viii, $MeSO_2Cl$, LiCl, *s*-collidine, DMF, 0 °C, 2 h (60%).†

extended dienoic acid side chain and probably serves as a biosynthetic precursor to the domoilactones A and B[2c] containing a β-hydroxybutyrolactone substituent which are found in the same algal source, while a rather different organism, the fungus *Clitocybe acromelalga* Ichimura, produces the acromelic acids A and B,[6] in which the C-4 substituent is a pyridonecarboxylic acid function. Early syntheses of racemic kainic[7] and allokainic[8] acids were relatively inefficient and non-stereoselective; however, a recent series of studies by Oppolzer and co-workers have culminated in highly enantioselective syntheses of both (−)-α-kainic acid (**1**)[9] and (+)-α-allokainic acid (**2**)[10] in which the crucial step is enantioselective formation of the C-3 to C-4 bond by an intramolecular ene reaction. Formation of this bond is also the key step in a radical-mediated approach which leads to optically pure samples of both acids [(**1**) and (**2**)], after separation of an epimeric mixture obtained from the cyclisation step.[11] Two non-stereoselective syntheses of racemic α-allokainic acid have been developed in which the pyrrolidine ring is established using [1,3]dipolar cycloaddition reactions of azomethine ylides.[12] Herein, we report an enantiospecific route to (−)-α-kainic acid (**1**), in which the key step is also formation of the C-3 to C-4 bond[9–11] but using an enolate Claisen rearrangement of a suitable azalactone. Previous studies[13] have shown that such rearrangements proceed exclusively *via* a boat-like transition state when the lactone is eleven-membered or smaller. A retrosynthetic analysis based on this finding is outlined in Scheme 1. The pyrrolidine (**3**) should be formed by Claisen rearrangement of the optically active azalactone *O*-silyl enolate [(**4**); R^2=Si-Bu^tMe_2] derived from the allylic chloride (**5**) and a β-amino-acid derivative (**6**) obtainable from L-aspartic acid (**7**). The anticipated positioning of the CH_2OR^1 substituent in enolate (**4**) pseudoequatorially as shown should result in high chiral induction into the two newly created asymmetric centres in heterocycle (**3**), conversion of which into acid (**1**) should be relatively straightforward.

Therefore, L-aspartic acid (**7**) was converted, in five steps, into the protected β-amino-acid derivative (**8**), $[\alpha]_D^{27}$ −16.7° (*c* 1.42, CH_2Cl_2) (Scheme 2), using established methodology. Of a number of protecting groups tried, the tri-isopropylsilyl (TIPS)[14] proved to be the most suitable for masking the hydroxymethyl function. [We anticipated a requirement for relatively robust protecting groups as these would have to survive a number of transformations including a lactonisation procedure during which *N*-t-butoxycarbonyl (Boc) groups are removed;[13] hence also the use of an ethoxycarbonyl function to block the nitrogen in acid (**8**).] The required (*Z*)-geometry of the allylic chloride (**5**) (Scheme 1) was realised by conjugate addition[15] of lithium dimethylcuprate to the butynoate (**9**) (Scheme 2), which gave only the (*Z*)-butenoate (**10**); subsequent reduction and chlorination then provided the desired chloride (**11**). The two fragments [(**8**) and (**11**)] were coupled together using a previously developed procedure[13] (Scheme 3)† leading to the homologue (**12**). Removal of the tetrahydropyranyl (THP) protecting group and lactonisation[16] of the resulting hydroxy-acid gave the azalactone (**13**), $[\alpha]_D^{27}$ +15.2° (*c* 1.41, CH_2Cl_2) in 40% yield for the two steps. The crucial Claisen rearrangement proceeded smoothly but only when the base (lithium di-isopropylamide, LDA) and the trapping agent (Bu^tMe_2SiCl) were pre-mixed[17] at low temperature before addition of the lactone (**13**). The actual rearrangement occurred as the reaction mixture was warmed to ambient temperature. Hydrolysis of the resulting silyl ester under mildly basic conditions gave the desired pyrrolidinecarboxylic acid (**14**), $[\alpha]_D^{27}$ −36.1° (*c* 1.68, CH_2Cl_2) in 55% overall yield. The spectroscopic data were consistent with the *relative* stereochemistry shown and thus with the expected

† Yields in parentheses refer to pure, isolated compounds which exhibited satisfactory spectroscopic and analytical data.



Scheme 3. *Reagents*: i, (**8**) + Bu^{n}Li (2 equiv.), THF, −78 → 0 °C, add Me_2SO, then (**11**), 20 °C, 16 h (70%); ii, pyridinium toluene-*p*-sulphonate, MeOH, 60 °C, 8 h (95%); iii, 2-chloro-1-methylpyridinium iodide, MeCN, 80 °C, 18 h (42%); iv, LDA (2 equiv.), Bu^tMe_2SiCl (2 equiv.), THF, −100 → 20 °C; v, K_2CO_3, MeOH–H_2O, 20 °C, 2 h (55% for iv + v); vi, (a) $(COCl)_2$, Et_2O, DMF (cat.), 0 → 20 °C, 2 h, (b) CH_2N_2, Et_2O, 0 → 20 °C, 16 h, (c) $PhCO_2Ag$ (cat.), Et_3N, MeOH, 20 °C, 16 h, (67%); vii, 40% aq. HF, THF, 20 °C, 6 h (90%); viii, Jones oxidation (62%); ix, Me_3SiI, C_5H_5N, $CHCl_3$, 60 °C, 5 h; x, KOH, H_2O, 20 °C, 16 h (70% for ix + x).†

intermediacy of the boat-like transition state (**4**) (Scheme 1) during the rearrangement. No isomers of the acid (**14**) were detected and hence complete chiral induction had occurred. Arndt–Eistert homologation of the acid (**14**) proceeded smoothly to give the pyrrolidineacetic acid ester (**15**), $[\alpha]_D^{27}$ −35.9° (*c* 1.38, CH_2Cl_2) which was desilylated and oxidised to give the acid (**16**), $[\alpha]_D^{27}$ −60.9° (*c* 0.35, CH_2Cl_2). Finally the *N*-ethoxycarbonyl group was removed using trimethylsilyl iodide and the remaining methyl ester hydrolysed by aqueous potassium hydroxide; following purification by ion-exchange chromatography and crystallisation from water, (−)-(α)-kainic acid (**1**) was isolated in 70% yield from acid (**16**). The synthetic material, m.p. 246—248 °C (decomp.), $[\alpha]_D^{27}$ −13.3° (*c* 0.36, H_2O) was identical to authentic material (Aldrich) according to its m.p. (authentic: 248—250 °C; mixed: 247—249 °C), optical rotation, and spectroscopic data (^1H and ^{13}C n.m.r., i.r., mass). Examination of other column fractions and the mother liquors from the final crystallisation showed that no other isomers were present. This approach to kainic acid is therefore enantiospecific and should be applicable to the elaboration of many analogues having the same absolute configuration as the parent compound.

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