

The total synthesis of (–)- α -kainic acid using titanium-mediated diene metallabicyclisation methodology

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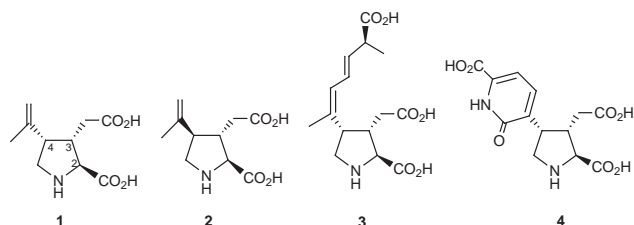
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Titanium-mediated diene metallabicyclisation–elimination–functionalisation has been utilised for the preparation of *syn*-3,4-disubstituted and *syn,syn*-2,3,4-trisubstituted pyrrolidines in high yield and excellent stereoselectivity; this methodology has been employed in a total synthesis of (–)- α -kainic acid starting from L-serine.

(–)- α -Kainic acid **1**, isolated from the marine algae *Digenea simplex*¹ and *Centrocerus clavulatum*² and from the Corsican



moss *Alsidium helminthocorton*,³ has generated a great deal of interest because of its potent neuroexcitatory activity. With the discoveries of α -allokainic acid **2**, the domoic acid family (e.g. domoic acid **3**) and the acromelic acid family (e.g. acromelic acid **4**), the synthetic community has been stimulated to design efficient, stereocontrolled routes to 2,3,4-trisubstituted pyrrolidines.⁴

Given our interest in the kainoid area,⁵ and our ongoing research into synthetic applications of diene metallabicyclisation reactions,⁶ we envisaged a new approach to kainic acid as shown in Scheme 1. Thus, zirconium- or titanium-mediated metallabicyclisation of diene **5** should produce the metallabicycle **6** which would be expected to undergo rapid β -elimination to generate the archetypal kainoid 4-isopropenyl substituent. This sequence would produce organometallic reagent **7** which could then be functionalised to introduce the requisite 3-carboxymethyl substituent of the kainoids.

Other cyclisation–elimination approaches to the kainoids have been investigated but stereochemical control has been poor.⁷ Similar problems were encountered when we explored the zirconium-mediated sequence outlined in Scheme 1, although a successful synthesis of (–)- α -kainic acid was accomplished.⁸ Here we describe the use of Sato's (η^2 -

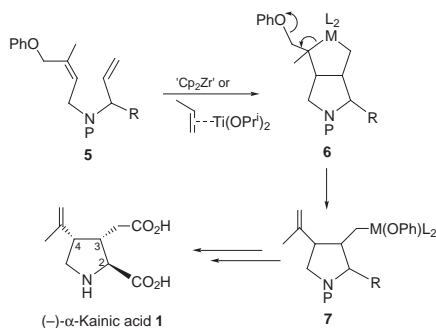
propene)Ti(OPrⁱ)₂ reagent⁹ in the metallabicyclisation–elimination sequence, and demonstrate that the procedure produces 3,4-disubstituted and 2,3,4-trisubstituted pyrrolidines with extremely high stereoselectivity. We then describe the application of this methodology to the synthesis of (–)- α -kainic acid **1**: to the best of our knowledge, this is the first application of diene metallabicyclisation–elimination methodology in natural product synthesis.

Model studies were first carried out to assess the viability of the (η^2 -propene)Ti(OPrⁱ)₂ procedure for the stereoselective preparation of pyrrolidines (Table 1).[†] As can be seen (entry 1), treatment of diene **8** with Ti(OPrⁱ)₄/2 PrⁱMgCl produced, after protonation, the 3,4-disubstituted pyrrolidine **9a** in an excellent yield with a 6:1 ratio of *syn*:*anti* diastereomers. The alkyl–titanium intermediate could also be halogenated giving alkyl halides **9b** and **9c** in good yield.

Cyclisation of the trisubstituted alkenes **10** and **12** also proceeds efficiently and with excellent *syn*-selectivity giving **11** as the only product (entries 2 and 3). Further studies are in progress to rationalise this much improved stereoselectivity. We next looked at the titanium-mediated cyclisation–elimination reaction of the 2-methyl substituted system **13**. We were delighted to observe that in this case the high C-3/C-4 *syn*-selectivity was retained, as only the two separable diastereoisomers **14** and **15** were isolated.[‡] Remarkably,^{9c} the major product was the *syn, syn*-diastereomer **14** in which all three substituents were on the same face of the pyrrolidine. This stereochemical assignment was confirmed by comparison of the ¹H NMR spectra of **14** and **15** with **9a** and related systems,⁸ and

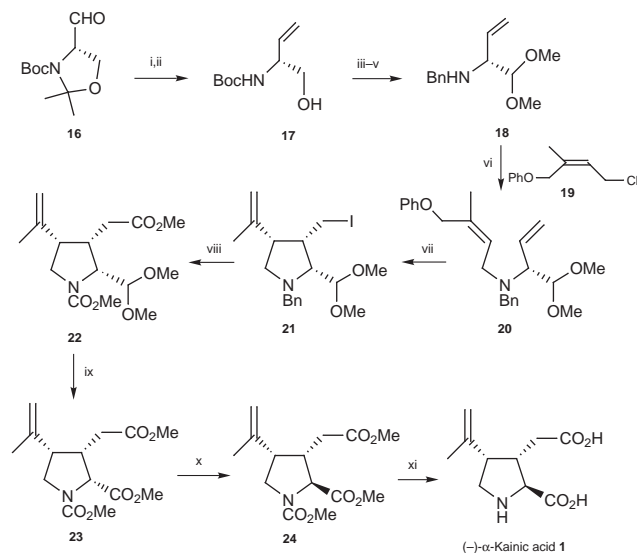
Table 1 Titanium-mediated diene metallabicyclisation–elimination–trapping reactions (*cis*:*trans* ratios determined by ¹H NMR spectroscopy)

Starting diene	Electrophile	Major product	Yield (%) (<i>syn</i> : <i>anti</i>)
1	PhO-CH=CH-CH=CH-Bn 8	H ⁺ (9a) I ₂ (9b) Br ₂ (9c)	 9a E = H, 85% (6:1) 9b E = I, 72% (6:1) 9c E = Br, 67% (6:1)
2	PhO-CH=CH-CH=CH-Bn 10	H ⁺	 84% (<i>syn</i> only)
3	PhO-CH=CH-CH=CH-Bn 12	H ⁺	 86% (<i>syn</i> only)
4	PhO-CH=CH-CH=CH-Bn 13	H ⁺	 14 and 15 74% 4:1



Scheme 1

by NOE studies (e.g. H-2 and H-4 enhanced by irradiation at H-3). It has been demonstrated that all *syn*-analogues of kainic acid can be epimerised at C-2 to give the kainoid structure.¹⁰ Thus, a titanium-mediated metallabicyclisation approach for the synthesis of kainic acid could commence with L-serine and include an epimerisation step after cyclisation. The strategy has now been implemented successfully (Scheme 2).



Scheme 2 Reagents and conditions: i, $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$ KHMDS, THF, -78°C (80%); ii, Dowex (H^+) resin, aq. MeOH (93%); iii, Dess–Martin oxidation; iv, HCl/MeOH ; v, PhCHO , $\text{NaBH}(\text{OAc})_3$, $\text{ClCH}_2\text{CH}_2\text{Cl}$ (31% for 3 steps); vi, K_2CO_3 , cat. NaI , MeCN, reflux (88%); vii, $\text{Ti}(\text{OPr})_4$, Pr^iMgCl (2 equiv.), Et_2O , -50°C to room temp., then I_2 , 0°C [56% (78% based on recovered **20**)]; viii, Bu^tLi (2.2 equiv.), Et_2O , -80°C , then excess ClCO_2Me , -80°C , then excess ClCO_2Me , $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux, 2 h (61%); ix, Jones' oxidation then CH_2N_2 (65%); x, LiHMDS (2.5 equiv.), THF, 0°C , then MeOH (80%); xi, NaOH/MeOH , reflux (70%).

Thus, L-serine was converted into the (*S*)-Garner aldehyde **16** using our improved procedure.¹¹ Wittig methylenation and acid hydrolysis gave the Boc protected vinylglycinol **17**^{11,12} which underwent Dess–Martin oxidation to a very unstable aldehyde which was immediately subjected to *N*-Boc deprotection–acetal formation to give an amino acetal which was then reductively aminated with benzaldehyde to give **18** in 31% yield over three steps. The ee of this amine was shown to be 93% by comparison with racemic material using HPLC on a chiral column [Chiralpak AS, 1:99 Pr^iOH –hexane, R_t 324 s (vs. 287 s)]. This is the first preparation of an acetal-protected vinylglycinol, a compound that could be useful in other synthetic applications. Alkylation with allyl chloride **19** then gave the cyclisation precursor **20** in 88% yield. § Allyl chloride **19** was prepared by Horner–Wadsworth–Emmons elaboration of 2-phenoxyacetone with methyl diethyl phosphonoacetate (94%, *E:Z* = 2:1) followed by chromatographic separation, reduction of the resulting α,β -unsaturated ester (DIBAL-H) and chlorination (TsCl , DMAP).

Ti^{IV} -mediated cyclisation–iodination of **20** gave the *syn,syn*-pyrrolidine **21** as the only cyclised product in 56% yield (78% based on recovered diene **20**). Lithium–halogen exchange and quenching with excess methyl chloroformate gave **22** in 61% overall yield. Jones' oxidation cleaved the acetal and oxidised the aldehyde produced to the corresponding acid which was treated with CH_2N_2 to give ester **23**. Compound **23** is a protected derivative of the so-called β -kainic acid: the titanium methodology provides a very convenient stereoselective route to these compounds which are reported to have interesting anti-convulsant properties.¹³

Epimerisation at C-2 was successfully achieved using LiHMDS (2.5 equiv.) and quenching with MeOH.^{10b} Using this

procedure, complete conversion into the epimeric ester **24** was observed [TLC (SiO_2 : EtOAc –light petroleum, 1:2) **23**, R_f 0.30; **24**,¹⁴ R_f 0.31]. Saponification of **24** was accompanied by *N*-deprotection giving (–)- α -kainic acid **1**, which was spectroscopically consistent with authentic material and corresponded well in terms of polarimetry [$[\alpha]_D -15.2$ (*c* 0.95, H_2O); lit.,¹⁵ -15.0 (*c* 0.5, H_2O)] and mp [mp 244 – 247°C (decomp.); lit.,¹⁵ mp 237 – 243°C (decomp.)].

In conclusion, we have developed a new enantioselective synthesis of (–)- α -kainic acid **1** which has as its cornerstone a totally stereoselective titanium-mediated diene metallabicyclisation process. The total synthesis is high yielding (3.5% in twelve steps from commercially available material). This new route contrasts to other cyclisation–elimination approaches to the kainoids where stereochemical control has been poor,⁷ and although our procedure does require epimerisation at C-2 to obtain the kainoid structure, it also provides a route to β -kainoids. In addition, kainoid analogues with a range of different substituents at C-3 and C-4 are available *via* this route. From a general methodological viewpoint, the new procedure for the stereoselective preparation of *syn,syn*-2,3,4-trisubstituted pyrrolidines is noteworthy.

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Notes and references

† All new compounds were fully characterised spectroscopically and by HRMS/elemental analysis.

‡ During the course of our studies Sato *et al.* also reported the stereoselective synthesis of a 2,3,4-trisubstituted pyrrolidine *via* titanium-mediated diene metallabicyclisation [ref. 9(c)], although their system was not suitable for elaboration to produce kainoids.

§ Initial studies were carried out with a protected alcohol as the C-2 substituent. Metallabicyclization was successful and completely stereoselective, but problems were encountered when trying to adjust the oxidation state of the C-2 substituent.

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