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

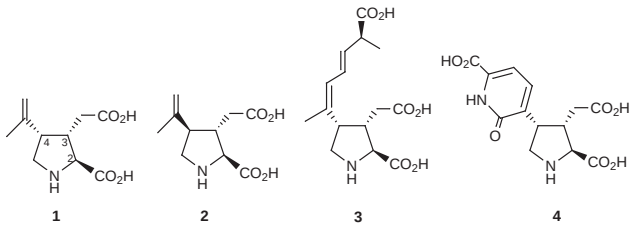
Andrew D. Campbell,[a] Tony M. Raynham[b] and Richard J. K. Taylor*[a]

[a] *Department of Chemistry, University of York, York, UK YO10 5DD. E-mail: rjkt1@york.ac.uk*
[b] *Roche Discovery Welwyn, Welwyn Garden City, Hertfordshire, UK AL7 3AY*

Received (in Cambridge, UK) 2nd November 1998, Accepted 11th December 1998

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

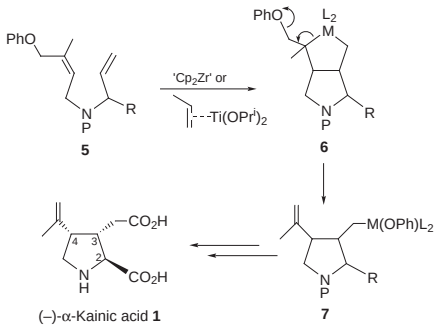


1 **2** **3** **4**

moss *Alsidum 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 A **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(OPr^i)$_2$ reagent[9] 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.

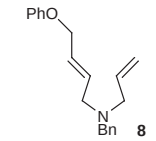
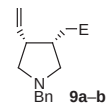
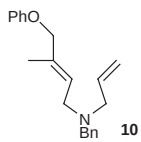
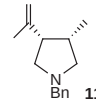
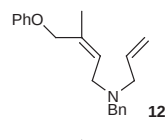
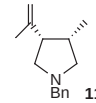
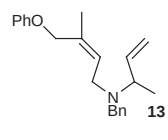
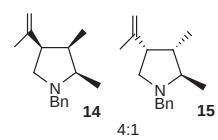


Scheme 1

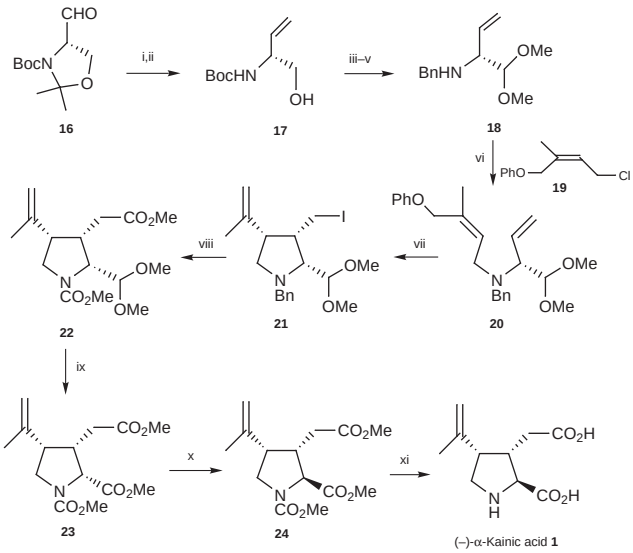
Model studies were first carried out to assess the viability of the (η_2-propene)Ti(OPr^i)$_2$ procedure for the stereoselective preparation of pyrrolidines (Table 1).† As can be seen (entry 1), treatment of diene **8** with Ti(OPr^i)$_4$/2 Pr^{i}MgCl produced, after protonation, the 3,4–disubstituted 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 ^{1}H 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 ^{1}H NMR spectroscopy)

	Starting diene	Electrophile	Major product	Yield (%) (*syn:anti*)
1	 **8**	H^+ (**9a**) I_2 (**9b**) Br_2 (**9c**)	 **9a–b**	**9a** E = H, 85% (6:1) **9b** E = I, 72% (6:1) **9c** E = Br, 67% (6:1)
2	 **10**	H^+	 **11**	84% (*syn* only)
3	 **12**	H^+	 **11**	86% (*syn* only)
4	 **13**	H^+	 **14** **15** 4:1	74%

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, $Ph_3P^+CH_3Br^-$ KHMDS, THF, −78 °C (80%); ii, Dowex (H^+) resin, aq. MeOH (93%); iii, Dess–Martin oxidation; iv, HCl/MeOH; v, PhCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$ (31% for 3 steps); vi, K_2CO_3, cat. NaI, MeCN, reflux (88%); vii, $Ti(OPr^i)_4$, 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 $ClCO_2Me$, $ClCH_2CH_2CI$, 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 vinylglycinal, 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^{II}-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.[10*b*] 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.

We are grateful to the BBSRC and Roche Discovery Welwyn for a CASE award (A. D. C.).

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.

1 S. Murakami, T. Takemoto and Z. Shimizu, *J. Pharm. Soc. Jpn.*, 1953, **73**, 1026.
2 G. Impellizzeri, S. Mangiafico, G. Oriente, M. Piatelli, S. Sciuto, E. Fattorusso, S. Magno, S. Santacroce and D. Sica, *Phytochemistry*, 1975, **14**, 1549.
3 G. Balansard, M. Pellegrini, C. Cavalli and P. Timon-David, *Ann. Pharm. Fr.*, 1983, **41**, 77.
4 A. F. Parsons, *Tetrahedron*, 1996, **52**, 4149.
5 A. F. Parsons and R. J. K. Taylor, *J .Chem. Soc., Perkin Trans. 1*, 1994, 1945.
6 A. J. Bird, R. J. K. Taylor and X. Wei, *Synlett*, 1995, 1237.
7 S.-E. Yoo, S.-H. Lee, K.-Y. Yi and N. Jeong, *Tetrahedron Lett.*, 1990, **31**, 6877; M.-P. Bertrand, S. Gastaldi and R. Nourguier, *Tetrahedron Lett.*, 1996, **37**, 1229; O. Miyata, Y. Ozawa, I. Ninomiya and T. Naito, *Synlett*, 1997, 275; see also M. D. Bachi and A. Melman, *J. Org. Chem.*, 1997, **62**, 1896.
8 A. D. Campbell, T. M. Raynham and R. J. K. Taylor, unpublished results.
9 (*a*) K. Harado, H. Urabe and F. Sato, *Tetrahedron Lett.*, 1995, **36**, 3203; (*b*) Y. Takayama, Y. Gao and F. Sato, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 851; (*c*) Y. Takayama, S. Okamoto and F. Sato, *Tetrahedron Lett.*, 1997, **38**, 8351.
10 (*a*) S. Takano, Y. Iwabuchi and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 1204; (*b*) A. Rubio, J. Esquerra, A. Escribano, M. J. Remuiñán and J. J. Vaquero, *Tetrahedron Lett.*, 1998, **39**, 2171.
11 A. D. Campbell, T. M. Raynham and R. J. K. Taylor, *Synthesis*, 1998, 1707; see also A. McKillop, R. J. K. Taylor, R. J. Watson and N. J. Lewis, *Synthesis*, 1994, 31 and references cited therein.
12 Z.-Y. Wei and E. Knaus, *Synthesis*, 1994, 1463.
13 J. F. Collins, A. J. Dixon, G. Badman, G. De Sarro, A. G. Chapman, G. P. Hart and B. S. Meldrum, *Neurosci. Lett.*, 1984, **51**, 371.
14 S. Takano, K. Inomata and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1992, 169.
15 W. Oppolzer and K. Thirring, *J. Am. Chem. Soc.*, 1982, **104**, 4978.

Communication 8/09598A