A New Enantioselective Route to Kainoids: Application to the Formal Synthesis of (−)-α-Kainic Acid

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The enantioselective synthesis of a 2,3,4-trisubstituted pyrrolidine featuring the kainoid C-2, C-3 *trans*, C-3, C-4 *cis* arrangement of substituents has been accomplished through a tandem Michael reaction strategy involving 2-nitro-3-methylbuta-1,3-diene as electrophilic alkene, the removable electron-withdrawing group acting as a template for control of the stereochemistry of the cyclization, together with a secondary benzylamine incorporating a chiral centre at the carbon bearing the nitrogen nucleophile and an appropriate α,β-unsaturated acceptor able to trap the initially formed nitronate.

We have previously described[1] a stereoselective entry to *trans*-3,4-disubstituted pyrrolidines based on a one-pot tandem Michael reaction methodology, involving an electrophilic alkene and a secondary benzylamine bearing an appropriately placed acceptor moiety which is able to trap the initially formed enolate. Incorporation of a chiral centre at the carbon atom bearing the nitrogen nucleophile as a tool for chirality transfer to the newly created contiguous centres at C-3 and C-4 expanded the scope of the protocol, ideally suited for a convergent enantioselective synthesis[2] of (+)- and (−)-α-allokainic acid **1**. However, most members of the kainoid family (*e.g.*, α-kainic acid, domoic acid, acromelic acids) possess as a common structural feature a trisubstituted pyrrolidine ring system with a C-2, C-3 *trans* and C-3, C-4 *cis* arrangement of substituents. Therefore we were compelled to investigate a suitable adaptation of the methodology for the preparation of 2,3,4-trisubstituted pyrrolidines having the required stereochemical orientation. A tactical solution would involve the reaction of the optically active fragment **2**, available in both enantiomeric forms starting from D- or L-serine,[2] with an electrophilic alkene bearing an electron-withdrawing group removable at a later stage as template for the control of cyclization stereochemistry. We now report how this goal has been reached and successfully demonstrated through a convergent formal synthesis of (−)-α-kainic acid **5**.[3]

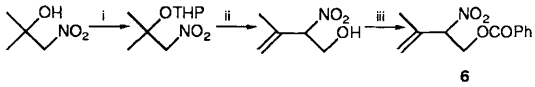
Having selected the nitro group as the electron-withdrawing group, and hence 2-nitro-3-methyl-buta-1,3-diene **3** as the ideal partner for the optically active fragment **2**, the crucial issue to be addressed was whether the tandem Michael reaction protocol would deliver the pivotal pyrrolidine intermediate **4** that could then be elaborated into the target. We were hopeful, but not certain, that the nitro group would offer sufficient steric interactions in the transition state leading to cyclization so that a favourable ratio of the desired product **4** with a *syn* relationship of the C-4 propenyl group to the C-3 acetic chain could be obtained. Besides the stereochemical outcome of the cyclization, an apparently trivial problem was immediately discernible: could we prepare the nitrodiene **3** or an equivalent thereof in a preparatively useful yield? The pyrolysis of 3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxide, the only reported preparation[4] of **3**, in view of its instability and propensity to anionic polymerization, was unsatisfactory in terms of both practicality and yield.

Fortunately we were able to prepare 1-benzoyloxy-3-methyl-2-nitrobut-3-ene **6**,† a suitable precursor for the electrophilic component **3** in the crucial coupling reaction with **2**, which acts both as donor–acceptor partner as well as basic catalyst for generating **3**. We were delighted to find that a quantitative yield of the desired pyrrolidine **4** could be obtained as sole product† simply by stirring at room temperature for 15 h equimolar quantities of **2** and **6** in ethanol. The extent to which the nitro group served as a crucial stereo- and regio-chemical control element during the cyclization is noteworthy.

The depicted stereochemistry agrees with the ^{1}H NMR spectrum, which exhibits two broad singlets for the alkene protons, indicating the *cis*-relationship of the acetic acid chain

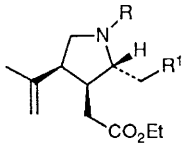
† All new compounds gave satisfactory analytical and spectroscopic data. The following compounds showed the indicated rotations, $[\alpha]_D^{20}$ (in $CHCl_3$), unless otherwise stated: **4**, −1.11° (*c* 2.19); **7**, −3.66° (*c* 0.75); **8**, −27.2° (*c* 0.99); **9**, −33.07° (*c* 0.61, CH_2Cl_2).

Compound **6** was prepared in 65% overall yield through the following steps:



6

Reagents and conditions: i, dihydropyran, *p*-$MeC_6H_4SO_3H$, CH_2Cl_2, −18°C; ii, $(CH_2O)_3$, MeONa, MeOH; iii, PhCOCl, C_6H_6, reflux; THP = tetrahydropyran-2-yl



7 R = $PhCH_2$; R^1 = OH
8 R = $PhCH_2$; R^1 = $OSiMe_2Bu^t$
9 R = Boc; R^1 = $OSiMe_2Bu^t$

and the isopropenyl appendage.[5] Further support to this assignment was obtained by formal conversion of **4** to (−)-α-kainic acid **5** as described below.

Having served its stereocontrolling role, the allylic nitro group was removed regio- and stereo-selectively by a hydride-transfer reaction in the presence of a palladium catalyst following Ono's procedure,[6] producing **7** in practically quantitative yield. While the regiochemistry is secured by use of ammonium formate as hydride source, stereoselectivity results from expulsion of nitrite ion from the π-allylpalladium complex and subsequent hydride attack.

The formal synthesis of (−)-α-kainic acid was then completed by prior standard protection of the hydroxy group of **7** as the *tert*-butyldimethylsilyl ether **8**, followed by removal of the nitrogen benzyl protective group and reprotection with Boc in a single operation,[7] affording a 50% overall yield of the intermediate **9**, already converted by Oppolzer *et al.*[3a] into (−)-α-kainic acid **5** along a totally different route.

In summary, the enantioselective tandem Michael reaction methodology provides convenient access to stereochemically defined 2,3,4-trisubstituted pyrrolidines, allowing the formation of three contiguous stereogenic centres with complete stereoselectivity in a single stage.

Thanks are due to Consiglio Nazionale delle Ricerche (C. N. R., Roma), Piano Finalizzato Chimica Fine e Secondaria II, for financial support of this work.

Received, 3rd December 1990; Com. 0/05434H

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