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ENANTIOSELECTIVE SYNTHESIS OF (+)- and (-)-α-ALLOKAINIC ACID

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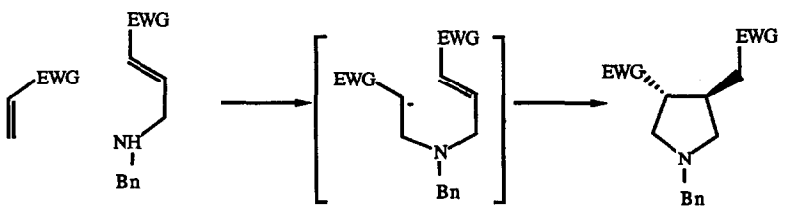
Summary A concise enantioselective route to (+)- and (-)-α-allokainic acid from D- and L-serine respectively has been established by enantio- and diastereo-selective tandem Michael reaction methodology for the construction of three chiral centers in a single stage.

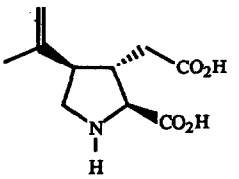
The development of new stereocontrolled approaches to substituted pyrrolidines is currently of interest, principally because these heterocyclic units are found in a wide range of biologically important natural compounds.

We have recently described[1] a stereoselective preparation of *trans*-3,4-disubstituted pyrrolidines based on a one-pot tandem Michael reaction methodology, involving an electrophilic olefin and a secondary benzylamine bearing an appropriately placed acceptor moiety able to trap the initially formed enolate, as outlined in the following scheme.



To extend this work to the synthesis of optically active substituted pyrrolidines we needed to induce specific chirality into the conjugate addition that established the chiral centers at C-3 and C-4. Thus we decided to incorporate a chiral center at the carbon bearing the nitrogen nucleophile as a tool for chirality transfer to the newly created contiguous centers at C-3 and C-4.

We now describe how this chemistry can be successfully addressed to the preparation of stereochemically defined trisubstituted pyrrolidines, which represent versatile chiral building blocks for the synthesis of biologically active natural products. As an example we report in this letter an enantioselective synthesis[2] of (+)- and (-)-α-allokainic acid **1**, which co-occurs[3] with its C-4 epimer, (-)-α-kainic acid **2**, in the marine alga *Diginea simplex* Ag.



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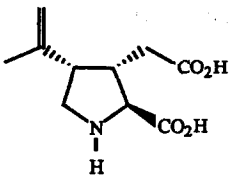
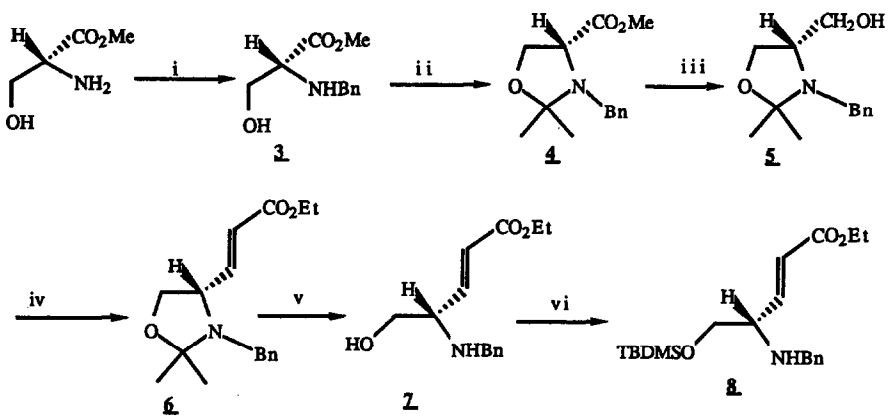


2

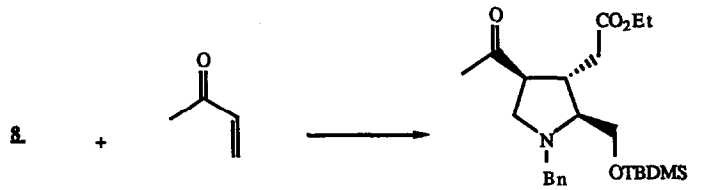
After having selected of methyl vinyl ketone as the electrophilic olefin considering the acetyl group as a logical precursor of the isopropenyl moiety, the first subgoal of our plan was the synthesis of the optically active donor-acceptor fragment 8*. This task was accomplished in 40% overall yield for six steps as illustrated in the following scheme starting from D-serine methyl ester which serves for the total synthesis of (+)-α-allokainic acid. We anticipated the inversion of configuration of the carbon bearing the hydroxymethyl group destined to become the carboxylic acid group of the natural target during these transformations.



Reagents: i, benzaldehyde, then $NaBH_4$; ii, 2,2-dimethoxypropane, H^+; iii, $LiAlH_4$; iv , DMSO, $(COCl)_2$, then $Ph_3P{=}CHCO_2Et$; v, HCl dil.; vi, TBDMSCl, Et_3N, DMAP.

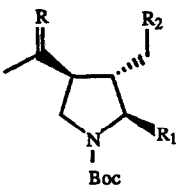
With the two partners in hand, the stage was set for the anticipated tandem Michael reaction protocol, which was carried out by allowing to react at room temperature the protected γ-amino-α,β-unsaturated ester 8** and methyl vinyl ketone in ethanol. The reaction proceeded rather slowly furnishing after 15 days the expected pyrrolidine 9 possessing the required C-2, C-3 and C-3, C-4 anti-

stereochemistry, the arrangement of lower steric interactions originated as previously reported[1] through an antiperiplanar orientation between the acceptor chain and the acetyl group in the intramolecular Michael reaction .



9

In order to expedite the cyclization of the initially formed intermolecular adduct we found it advantageous to add a few drops of tetramethylguanidine (TMG) after the disappearance of the starting materials. Alternatively the reaction can be carried out in two separate steps by adding $FeCl_3$ not only as a catalyst for the intermolecular Michael addition between the α,β-unsaturated ketone and **8** , but also as an inhibitor for the intramolecular process.[4] The subsequent cyclization could be promoted by TMG as well as by other bases such as sodium ethoxide giving rise to **9** in 90% yield.



10 R=O; R_1=$CH_2OTBDMS$; R_2=CO_2Et

11 R=CH_2; R_1=$CH_2OTBDMS$; R_2=CO_2Et

12 R=CH_2; R_1=CH_2OH; R_2=CO_2Et

13 R=CH_2; R_1=CO_2H; R_2=CO_2Et

Hydrogenolytic removal of the nitrogen protective group and reprotection as Boc were carried out in a single operation following reported directions[5] affording **10** in practically quantitative yield. Wittig olefination of the latter (60%) introduced the C-4 isopropenyl moiety and the oxidation state at C-2 substituent was adjusted by cleavage of the silyl ether group of **11** by treatment with tetrabutylammonium fluoride (85%) and subsequent oxidation of the resulting primary alcohol **12** with Jones reagent to furnish the carboxylic acid **13** (55%).

Saponification of **13** with LiOH followed by removal of *tert*-butoxycarbonyl group with trifluoroacetic acid and final treatment of an aqueous solution of the evaporated reaction mixture with ion-exchange resin allowed the isolation of enantiomerically pure (+)-α-allokainic acid (56%) after recrystallization from water.

The synthetic material, m.p.238-242°C, $[\alpha]^{20}_D$ +7.77(c 0.18 ,H_2O), was identical to authentic material according to its m.p., spectroscopic data and optical rotation $[\alpha]^{23}_D$ +7.4(c 0.7 ,H_2O).[2a] The same sequence applied to the enantiomer of **8**, in turn obtained starting from L-serine methyl ester, allowed to obtain (-)-α-allokainic acid. In summary this approach to (+)- and (-)-α-allokainic acids further illustrates the potential of the tandem Michael reaction protocol for the enantioselective synthesis of stereochemically defined pyrrolidines.

We are now actively looking for a suitable device for an extension of the present strategy to all kainoids.

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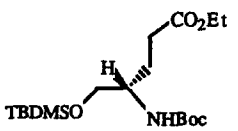
* IR, ^1H and ^{13}C NMR (200MHz) and mass spectra are in full agreement with the assigned structures. The following compounds showed the indicated rotations $[\alpha]^{20}_D$ (in $CHCl_3$): **8**, +5.96(c 0.95); **9**, -81.3(c 0.91); **10**, -4.64(c 1.68); **11**, -8.4(c 1.07); **12**, -9.4(c 1.04); **13**, -8.75 (c 0.41).

** Hydrogenation (5% C/Pd) of **8** in the presence of $(Boc)_2O$ led directly to the known **i**, $[\alpha]^{20}_D$ -22.5(c, 0.88, CH_2Cl_2) , prepared from S-glutamic acid and already taken to (-)-α-kainic acid: (W. Oppolzer and K. Thirring, J. Am. Chem. Soc., 1982, **104**, 4978.), thus establishing unambiguously its optical integrity.



i

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