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A Concise Approach to Kainoid Analogues

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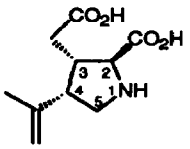
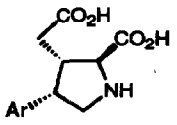
Abstract: Highly neuroexcitatory kainoid analogues bearing an aryl substituent at C-4 were synthesised by a short and efficient route from *trans-L*-4-hydroxyproline

Recently, much interest has been focused on the synthesis of the kainoids, a class of interesting non proteinogenic amino acids[1]. The kainoids exhibit a powerful neuroexcitatory activity[2] and it has been reported, that introduction of an aryl substituent at C-4 of the pyrrolidine ring effects a strong potentiation of this activity[3,4].



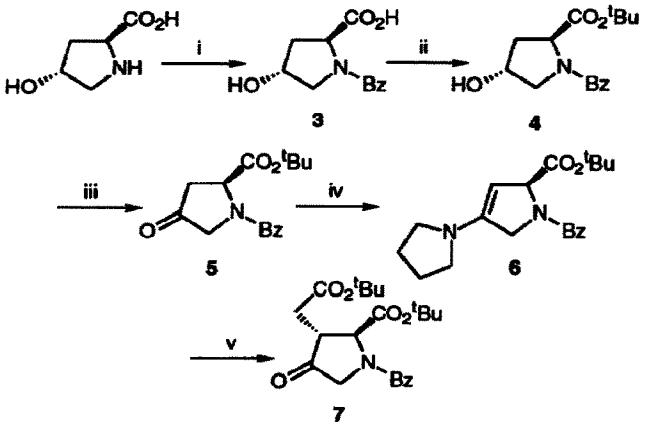
1
Kainic Acid



2
4-Aryl Kainoid Derivative

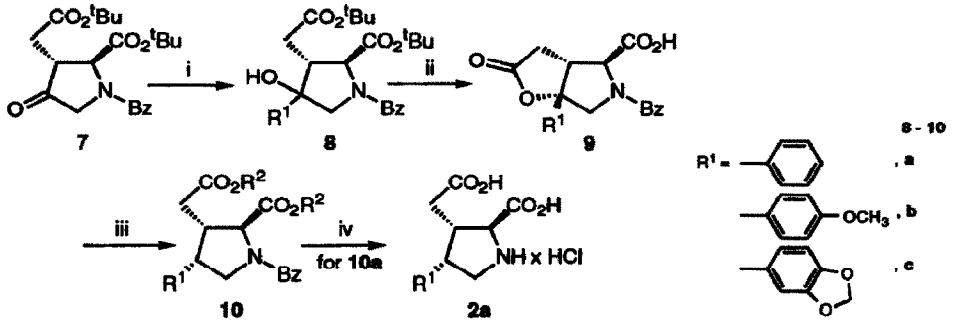
In our continuing interest in the synthesis of kainic acid (1) and related species we tried to establish a short and general synthetic route to compounds of type **2** . A common feature to all kainoids is the (2*S*, 3*R*, 4*R*)-stereochemistry, the 2,3-*trans* relationship usually being easily achieved synthetically, unlike the more demanding 3,4- *cis* stereochemistry.

The cheap, commercially available *L-trans*-4-hydroxyproline seemed to be ideally suited as starting material, providing the correct stereochemistry at C-2 and an access to C-3 and C-4 *via* the 4-hydroxy group. Thus, *L-trans*-4-hydroxyproline was N-protected with benzoyl chloride/sodium hydroxide to give the *N*-benzoyl derivative **3** in very high yield[5]. The free acid was converted into the *t*-butyl ester **4** by reaction with *t*-butanol and dimethylformamide dineopentylacetal in refluxing benzene without any detectable amount of the undesired 4-*t*-butyl ether[6].Oxidation of the secondary alcohol with sodium periodate with ruthenium(VIII) oxide catalysis gives the 4-oxoproline derivative **5** in excellent yields[7,8].



i) C_6H_5COCl, Et_2O/ NaOH (1N), 89%; ii) ^tBuOH, benzene, DMF-dineopentylacetal, reflux, 82%; iii) $NaIO_4$, $RuO_2 \cdot H_2O$, H_2O, CCl_4, $CHCl_3$, 97%; iv) Pyrrolidine, benzene, molsieves 5Å, quant.; v) 1)$BrCH_2CO_2{}^tBu$, CH_3CN, K_2CO_3; 2)H_2O, CH_3CO_2H, 53%.

Previous studies have shown, that enamine formation using 4-oxoproline derivatives and pyrrolidine leads to almost complete formation of the 3,4-dehydro species, which can be alkylated regiospecifically in 3-position[9]. Thus, ketone **5** was treated with pyrrolidine in benzene (16h, rt, molsieves 5Å[10]) to yield quantitatively enamine **6** with the predicted regiochemistry. **6** shows a strong absorption at 1646 cm^{-1}, indicating the complete formation of the enamine. NMR studies indicate, that the product consists of at least 95% the desired 3,4-dehydro isomer.



i) R^1MgBr, Et_2O, 43 - 52% or R^1Li, $CeCl_3$, THF, Et_2O, 43 - 67%; ii) CF_3CO_2H, quant.; iii) 1)H_2, Pd/C, MeOH, $R^2 = H$; 2) $(C_6H_5)_2CN_2$, R^2 = Bzh, 18 - 66%; iv) HCl (6N), reflux, 90%.

Enamine **6** proved to be an excellent substrate for alkylations in the 3-position. Thus, the desired substitution pattern at C-3 could be obtained by reacting **6** with *t*-butyl bromoacetate, followed by hydrolysis

of the enamine, to give the alkylated ketone **7** in fair yields. The *trans*-stereochemistry was proved by NOE-experiments at elevated temperature.

Introduction of the C-4 substituent was achieved through the Grignard reagent. In THF competing enolisation towards C-3 permitted isolation of carbinol **8** in only poor yield. However, in diethyl ether a single diastereomeric carbinol could be obtained (*ca.* 50 % yield) and similar yields of a mixture of diastereomers were achieved through organocerium reagents in THF/diethylether[11].

Treatment of the carbinols **8** with trifluoroacetic acid effected cleavage of the *t*-butyl esters and concomitant lactonization to a single *cis*- fused bicyclic lactone **9**, quantitatively. Both diastereomers at C-4 gave the same lactone **9**. This lactone was smoothly hydrogenolyzed (Pd/C), with inversion[12], to the diacid (**10**, R^2 = H), which was purified as the bis-benzhydrylester (**10**, R^2 = Bzh) and finally hydrolyzed (**10a**) with 6N HCl to the kainoid hydrochloride **2a**[13].

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13 Spectroscopical data for **2a**: ^{1}H NMR(D_2O, 500 MHz): δ = 2.29 (dd, J = 9, 17 Hz, 1H, CHC$\underline{H}_2$), 2.61 (dd, J = 6, 17 Hz, 1H, CHC$\underline{H}_2$), 3.28 (m, 1H, C(3)-H), 3.79 (dd, J = 8, 11 Hz, 1H, C(5)H_2), 3.94 -4.03 (m, 2H, C(5)H_2+C(4)-H), 4.22 (d, J = 7 Hz, 1H, C(2)-H), 7.25 - 7.27 (m, 2H, H_{arom}), 7.39 - 7.45 (m, 3H, H_{arom}) ppm. ^{13}C NMR (D_2O, 126 MHz): δ = 34.5 (CH$\underline{C}H_2$), 43.7 (C-3), 45.7 (C-4), 49.2 (C-5), 65.8 (C-2), 129.0, 129.5, 130.0, 136.7 (C_{arom}), 173.3, 176.2(C=O) ppm. IR (KBr): 3360 - 3520, 2960, 2922, 1722, 1630 cm^{-1}. MS (electrospray): m/z = 250 (100 %, M+1). $[\alpha]_D^{20}$ = + 14.3 (c = 0.3, H_2O). mp = 327 - 332 °C (dec).

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