Synthesis of Kainoids via a Highly Stereoselective Hydroformylation of Kainic Acid

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Abstract: An efficient preparation of a series of secondary amines, structurally related to the kainic acid scaffold, is described. Naturally occurring (–)-α-kainic acid was hydroformylated with complete terminal selectivity and high stereoselectivity. The stereochemistry of the product was investigated through the ROESY and HETLOC spectra of the corresponding 2,4-dinitrophenyl hydrazone, showing the presence of a single diastereoisomer with rotamers related to the presence of the Boc group. The aldehyde was used as a platform to prepare amines by reductive amination in ionic liquids.

Key words: hydroformylation, natural products, ionic liquids, heterocycles

As a result of recent advances in molecular biology, there is presently a high demand for drug-like small molecules.[1] Natural products are considered as a rich source of lead structures in the search of bioactive molecules,[2] and are often used as original scaffolds for the generation of libraries of compounds through decoration processes, which introduce functionalities for further chemical elaborations.[3] In addition natural products have been used to elucidate complex cellular mechanisms, leading to the identification of important tools for therapeutic intervention. Consequently, the incorporation of natural products in chemical libraries is an expanding tactic in medicinal chemistry.[4]

Looking for possible applications of this concept, we were particularly intrigued by the possibility of using kainic acid (**1**) as a scaffold of natural origin. The kainoid family displays potent specific anthelmintic, insecticidal and neuroexcitatory activities.[5] Members of this family act as agonists of two subtypes of ionotropic glutamic receptors (Ka and AMPA) and play an important role in the regulation of the level of L-glutamic acid (Glu), the primary excitatory neurotransmitter in the mammalian central nervous system.[6] As the function of kainic receptors is still elusive, the identification of new ligands could be essential for the elucidation of the role of these receptors.

The presence of different functional groups, two carboxylates, a basic nitrogen and an alkene, which can be further elaborated, makes compound **1**, commercially available, uniquely suited for synthesis of analogues. Although an obvious strategy for decoration would be the transformation of the carboxylates or the amino groups, we decided to take advantage of the presence of the isopropenyl moiety at C-4 in kainic acid (**1**). In the past, several groups have reported various modifications on this part of compound **1** through arylation via Heck type chemistry,[7] allylic oxidation or ozonolysis.[7,8] This last transformation has been extensively applied by Baldwin's group for the elaboration of various heterocycles at C-4 using the chemical potential of the corresponding methyl ketone.[9] As the C-4 stereocenter bearing a methyl ketone in the kainoids was found to be extremely labile even during the purification step,[10] we decided to try a hydroformylation of the double bond at C-4. The functionalization would be removed from the stereogenic center, thus preventing possible epimerization. Moreover, the presence of an aldehyde in the molecule would open several new possibilities, by virtue of the chemical potential of the carbonyl functionality.

Herein, we describe the synthesis of new enantiopure kainoids substituted at C-4, obtained from (–)-α-kainic acid via aldehyde **3**, synthesized by hydroformylation of the double bond, a well-established synthetic device for the preparation of aldehydes. In the hydroformylation of alkenes regioselectivity has crucial importance, as linear or ramified aldehydes can be obtained. In our case, only the terminal aldehyde (**3**) is targeted and the presence of a methyl residue on the double bound will give rise to the formation of a new stereocenter at C1′. Therefore, we have to address which is the best catalyst for the synthesis of the linear aldehyde **3** and whether diastereoselection could be achieved in the hydroformylation process.

In order to prepare the substrate for the reaction of hydroformylation, kainic acid (**1**) was transformed into its dimethyl ester, using chlorotrimethylsilane in refluxing methanol for four hours followed by conversion to the *N*-Boc-derivative using standard conditions.[9] This two-step procedure gave compound **2** in very good overall yields (80% after chromatography, Scheme 1).
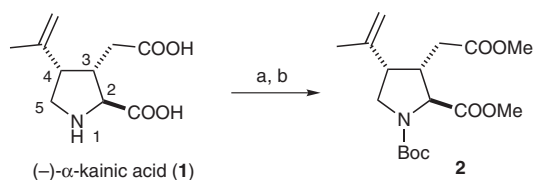
Scheme 1 Protection of kainic acid. *Reagents and conditions*:
a) MeOH, Me₃SiCl, 80 °C, 4 h; b) Boc₂O, Et₃N, MeOH–THF, r.t.

Hydroformylation of **2** was first attempted using a Rh(CO)₂acac–PPh₃ complex as catalyst, and only a modest linear/branched selectivity (**3a–b**, 65:35) was obtained (Scheme 2). The ratio of the two regioisomeric aldehydes could be easily monitored by examination of the proton signal multiplicity of the aldehyde proton, which appeared as a triplet in compound **3a** and as a singlet in compound **3b**. Exploration of other experimental conditions showed that the catalytic system HRh(CO)(PPh₃)₂ Xantphos[11] (under 20 bar of H₂/CO, 1:1 at 40 °C for 72 h) allowed a highly selective hydroformylation. Using this procedure we obtained exclusively the terminal isomer **3a**, isolated in 85% yield after flash chromatography. On the other hand, terminal hydroformylation of **2** generated a new stereocenter and the diastereoselectivity of the process required investigation. However, compound **3a** was not the ideal substrate for this kind of analysis due to the presence of a very reactive CHO group.
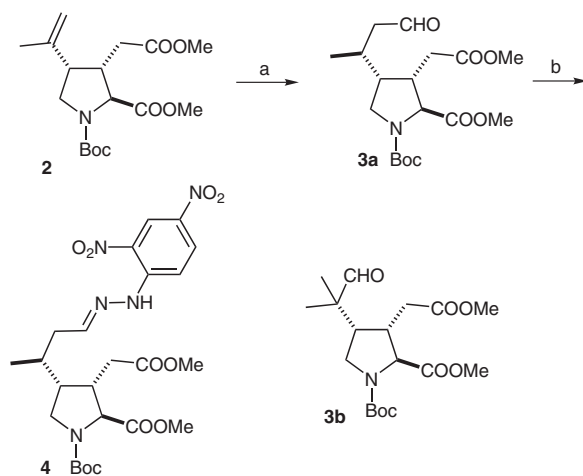

Scheme 2 Hydroformylation of kainic acid. *Reagents and conditions*: a) H₂, CO, HRh(CO)(PPh₃)₂/Xantphos 20 bar, 40 °C, 72 h; b) 2,4-dinitrophenylhydrazine, H₂SO₄ in MeOH.

The aldehyde **3a** was then converted to the corresponding 2,4-dinitrophenylhydrazone by the standard procedure (Scheme 2) and the resulting product **4** was submitted to detailed NMR studies showing that only one diastereoisomer was formed in the hydroformylation reaction of **2**.

RP-HPLC analysis of **4** on a C-18 column revealed the presence of a single broad peak. The ¹H NMR spectrum of a HPLC purified aliquot of **4** showed resonances attributable to a single pure compound, although selected spectral regions contained two distinct sets of signals, suggesting

that **4** was in fact characterized by different exchanging rotamers, slowly interconverting on the NMR timescale. Experimental evidence of chemical exchange came from the ROESY spectrum of **4** (600 MHz, CDCl₃, t$_{mix}$ = 400 ms), where exchange cross-correlations (with sign opposite to diagonal peaks) between pairs of interconverting signals were well evident. NMR analysis of **4** was completed by configurational assignment at C1′, the new stereocenter generated upon hydroformylation of **2**. For this purpose, we examined the C4-C1′ pair of adjacent stereocenters in light of the recently reported *J*-based method.[12] The pattern of ³*J*$_{C-H}$ couplings, extracted from HETLOC spectra,[13] allowed to rule out all the 3D arrangements with H4 and H1′ in *gauche* relationship, leaving out only two H4-H1′ *anti*-conformers with opposite relative configurations. The ROESY[14] spectrum contained key dipolar couplings that permitted to establish unequivocally the correct configuration of this molecular segment. Crucial to such configurational assignment were the ROE cross-peak between H3 and C1′-Me, the strong ROE effects between the C1′-Me and H₂-5 and between the H3 and the H₂-2′ The pattern of ROE effects observed in DMSO-d₆ was even more evident, giving additional support to our assignment. On the basis of these data, a *threo* (*syn*) relative arrangement can be established for the C4-C1′ pair; taking into account the *S* absolute configuration of C4 in the parent natural product, a C4-C1′ *threo* relative arrangement can be translated into the *R* absolute configuration for C1′. To find a rationale for the high diastereoselectivity in the hydroformylation reaction, a close examination of the conformers of the isoprenyl side chain at C-4 was carried out. Two distinct conformers (**2a** and **2b** in Scheme 3) can be postulated from molecular models. In **2a** the double bond is '*pseudo endo*' and in **2b** '*pseudo exo*' with respect to the five-membered ring. Therefore the allylic 1,2 strain favors conformer **2a** over **2b** by considering the van der Waals interactions between the pyrrolidine ring and, alternatively, the methylene (**2a**) or the methyl residues (**2b**).[15] The two hydrogen atoms at C-2 and C-5 contribute to destabilize conformer **2b**. Therefore hydroformylation takes place from the *si* face of the isopropylene residue producing **3a**.
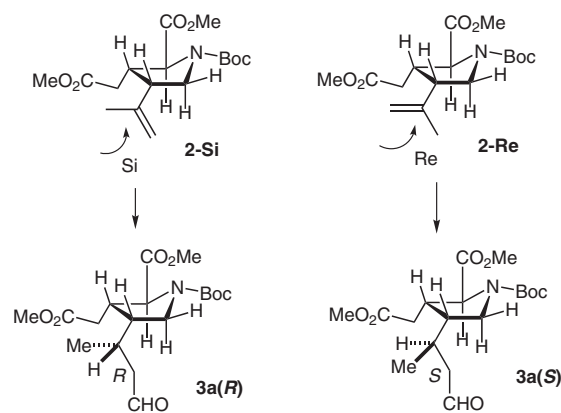
Scheme 3

With enantiopure aldehyde **3a** in hand, it is possible to generate molecular diversity by different approaches such as, for example, a reductive amination process, in view of its facile exploitation for parallel synthesis (Scheme 4).

5 R = -CH$_2$CH(CH$_3$)$_2$
80%

6 R =
74%

7 R =
76%

8 R =
OMe
OMe
78%
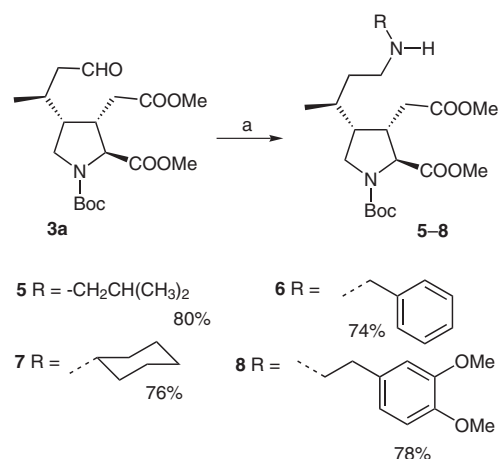
Scheme 4 *Reagents and conditions*: a) RNH$_2$, NaBH$_3$CN, [bmim][BF$_4$], r.t.

As proof of concept, we examined the feasibility of the reductive amination reaction by treating **3a** with isobutylamine in the presence of NaCNBH$_3$ employing MeOH as the solvent. Following these standard conditions, compound **5** was isolated in modest yield contaminated by several by-products. On the other hand, we were able to improve the amination reaction by changing the conditions and the nature of the reducing agent. In fact, when dry ionic liquid ([bmim][BF$_4$])[16] was used instead of the traditional solvents, the resulting amine **5** was obtained in 80% yield by extraction from the ionic medium with ethyl acetate. The product was around 90% pure (^{1}H NMR analysis) and could be additionally purified by flash chromatography. Encouraged by this result, we carried out the reductive amination with different amines and the kainoids **5–8** were obtained in good yields.

In conclusion, a highly regio- and stereoselective hydroformylation of kainic acid has been realized to afford aldehyde **3a**, which can be further elaborated by reductive amination in ionic liquid, opening new possibilities towards the synthesis of potential conformationally constrained and functionalized glutamic acid analogues, or kainoid derivatives.

1-(*tert*-Butoxycarbonyl)kainic Acid Dimethyl Ester (2, Adapted from Ref.[9] with Modifications)
Thionyl chloride (8.66 mmol) was added dropwise to MeOH (10 mL) at 0 °C. After the addition was complete, **1** (1 g, 4.3 mmol) was added and the reaction mixture warmed to 60 °C for 24 h. After removal of the solvent in vacuo, a white solid was obtained. This compound was suspended in CH$_2$Cl$_2$ (15 mL) and Et$_3$N (5.76 mmol) was added at r.t. (the pH must be kept around 10; if lower, more Et$_3$N must be added). A solution of (Boc)$_2$O (2 g, 9 mmol) in CH$_2$Cl$_2$ (10 mL) was then added, followed by DMAP (20 mg). The reaction was stirred at r.t. overnight. After removal of the solvent in vacuo, the residue was taken up in CH$_2$Cl$_2$ and the organic phase was dried and

Table 1 Characterisation of Kainic Derivative **4**

Position	δ_H (CDCl$_3$)	δ_C (CDCl$_3$)	δ_H (d_6-DMSO)	δ_C (d_6-DMSO)
1-Boc-CO	–	174.8	–	174.8
1-Boc-C	–	78.8	–	78.8
1-Boc-CH$_3$	1.40	27.6	1.32	27.6
2	4.17	64.4	4.04	63.9
2-CO	–	172.3	–	171.9
2-OCH$_3$	3.63	51.7	3.63	51.4
3	2.84	40.9	2.73	40.1
3-CH$_2$	2.50, 2.33	31.9	2.54, 2.31	31.6
3-CO	–	171.9	–	172.1
3-OCH$_3$	3.63	51.7	3.63	51.4
4	2.31	44.0	2.15	43.8
5	3.76, 3.10	48.2	3.55, 3.07	47.7
6	1.85	30.7	1.81	29.4
6-Me	1.04	18.0	0.92	17.6
7	2.52, 2.27	37.3	2.41, 2.17	36.8
8	7.52	149.1	8.01	153.3
NH	11.1	–	11.4	–
1'	–	144.6	–	144.5
2'	–	128.9	–	128.2
3'	9.13	123.2	8.85	122.9
4'	–	137.9	–	136.3
5'	8.33	129.7	8.35	130.1
6'	7.92	116.1	7.85	115.8

concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$–EtOAc (12:1) to give **2** (1.3 g, 90%) as a syrup: [α]$_D$ –16.2 (*c* 1.5, CHCl$_3$) {lit[7] [α]$_D$ –17.8 (*c* 1.2, CHCl$_3$)}. ^{1}H NMR (300 MHz, CDCl$_3$, 40 °C, mixture of rotamers): δ = 1.38 and 1.45 (9 H, 2 × s), 1.67 (3 H, s), 2.18–2.38 (2 H, m), 2.74–2.87 (1 H, m), 2.93–3.03 (1 H, m), 3.35–3.48 (1 H, m), 3.60–3.72 (1 H, m), 3.68 and 3.74 (2 × 3 H, 2 × s), 4.04 and 4.14 (1 H, 2 × d, *J* = 4.3 Hz),4.67 and 4.90 (2 × 1 H, 2 × s).^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 27.7 (3 C), 29.6, 30.9, 31.8, 41.4, 43.8, 47.9, 51.3 (2 C), 65.0, 78.8, 108.7, 123.4, 172.0, 171.3, 174.8.

Hydroformylation of 2

Compound **2** (1.2 g, 3.5 mmol) was dissolved in dry toluene (10 mL) and added to a slurry of HRh(CO)(PPh$_3$)$_3$ (60 mg) and Xantphos (144 mg, 4 equiv with respect to the Rh catalyst) in an autoclave. The reaction mixture was stirred at 40 °C at 20 bar H$_2$/CO 1:1 v/v pressure for 72 h. After cooling and careful degassing of the autoclave, the solvent was evaporated and the product **3a** isolated by flash chromatography (eluent CH$_2$Cl$_2$–EtAc, 9:1) giving 1.17 g, 90% yield. ^{1}H NMR (200 MHz, CD$_3$OD): δ = 0.92 (d, J = 7 Hz, 3 H), 1.42 and 1.36 (two rotamers, s, 9 H), 1.67–2.5 (m, 7 H), 3.07 (m, 2 H), 3.68 (s, 6 H) 4.21 (m, 1 H), 9.71 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 27.7 (3 C), 29.6, 31.9, 39.8, 41.4, 43.8, 47.9, 51.3 (2 C), 65.0, 78.8, 172.0, 171.3, 174.8, 194.6. MS (ES): m/z = 372 [M$^+$ + 1].

Reductive Amination in Ionic Liquid – General Procedure

Aldehyde **3a** (50 mg, 0.135 mmol) was mixed with freshly distilled amine (0.269 mmol) in dry [bmim][BF$_4$] (300 mg). Solid sodium cyanoborohydride (27.8 mg, 0.404 mmol) was added and the mixture was vigorously stirred at r.t. for 48–96 h. When the starting material disappeared (TLC analysis) the mixture was treated with 3 mL of a sat. aq NaHCO$_3$. The aqueous layer was extracted several times with EtOAc. The collected organic phases were dried over anhyd Na$_2$SO$_4$ and then purified by flash chromatography. The products **5–8** were obtained with 70–85% yields.

Compound **5**: oil; R_f = 0.32 (EtOAc–CH$_2$Cl$_2$, 4:1). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 4.20/4.05 (m, 1 H, H-2), 3.73 (s, 3 H, OCH$_3$), 3.72 (s, 3 H, OCH$_3$), 3.13–2.96 (m, A part of an ABX system, 1 H, H-5), 2.84–2.63 (m, B part of an ABX system, 1 H, H-5), 2.59–2.35 (m, 4 H, H$_2$-3′, 2 × NHCH$_2$), 2.32–1.96 (m, 6 H, H-3, CH$_2$COOMe, NH, NHCH$_2$CH, H-4), 1.76–1.63 (m, 1 H, H-1′), 1.60–1.34 (m, 11 H, Boc, H$_2$-2′), 0.98–0.81 [m, 9 H, CHCH$_3$, NHCH$_2$CH(CH$_3$)$_2$]. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 20.7 (2 C), 27.7 (3 C), 28.9, 29.6, 31.9, 39.8, 41.4, 43.8, 44.7, 47.9, 51.3 (2 C), 57.8, 65.0, 78.8, 172.0, 171.3, 174.8. ESI-MS: C$_{22}$H$_{40}$N$_2$O$_6$ [M + H]$^+$: 429. Anal. Calcd for C$_{22}$H$_{41}$ClN$_2$O$_6$ (hydrochloride): C, 56.8; H, 8. 9; Cl, 7.6; N, 6.0. Found: C, 56.4; H, 8.8; Cl, 7.7; N, 5.8.

Compound **6**: oil; R_f = 0.37 (EtOAc–CH$_2$Cl$_2$, 4:1). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C) δ = 7.21–7.04 (m, 5 H, Ph), 4.23–4.16 (m, 2 H, CH$_2$Ph), 4.12 (m, 1 H, H-2), 3.70 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, OCH$_3$), 3.24–3.05 (m, A part of an ABX system, 1 H, H-5), 2.87–2.68 (m, B part of an ABX system, 1 H, H-5), 2.64–2.46 (m, 3 H, H-3, H$_2$-3′), 2.40–1.88 (m, 4 H, CH$_2$COOMe, NH, H-4), 1.69–1.60 (m, 1 H, H-1′), 1.58–1.30 (m, 11 H, Boc, H$_2$-2′), 0.90/0.85 (m, 3 H, CHCH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 27.7 (3 C), 29.7, 31.3, 39.8, 41.4, 43.8, 44.7, 47.9, 51.3 (2 C), 55.3, 65.7, 78.4, 127.3, 128.8 (2 C), 129.1 (2 C), 136.1, 172.1, 171.3, 174.0. ESI-MS: C$_{25}$H$_{38}$N$_2$O$_6$ [M + Na]$^+$: 485. Anal. Calcd for C$_{25}$H$_{39}$ClN$_2$O$_6$ (hydrochloride): C, 60.2; H, 7.8; Cl, 7.1; N, 5.6. Found: C, 60.0; H, 7.6; Cl, 7.0; N, 5.4.

Compound **7**: oil; R_f = 0.31 (EtOAc–CH$_2$Cl$_2$, 4:1). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 4.16 (m, 1 H, H-2), 3.69 (s, 3 H, OCH$_3$), 3.67 (s, 3 H, OCH$_3$), 3.15–2.98 (m, A part of an ABX system, 1 H, H-5), 2.81–2.59 (m, B part of an ABX system, 1 H, H-5), 2.55–2.32 (m, 3 H, H$_2$-3′, NHCH), 2.32–1.96 (m, 4 H, H-3, CH$_2$COOMe, NH), 1.75–1.58 [m, 6 H, H-1′, H-4, NHCH(CH$_2$)$_2$], 1.49–1.31 (m, 17 H, Boc, H$_2$-2′, 3 × CH$_2$-cycloesil), 0.95/0.90 (m, 3 H, CHCH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 22.0 (2 C), 27.7 (3 C), 29.0, 29.6, 31.9, 34.8 (2 C), 39.8, 41.4, 43.8, 45.2, 47.9, 51.3 (2 C), 56.8, 65.0, 78.8, 172.0, 171.7, 174.2. ESI-MS: C$_{24}$H$_{42}$N$_2$O$_6$ [M + H]$^+$: 455. Anal. Calcd for C$_{24}$H$_{43}$ClN$_2$O$_6$ (hydrochloride): C, 58.7; H, 8.8; Cl, 7.2; N, 5.7. Found: C, 58.9; H, 8.7; Cl, 7.0; N, 5.5.

Compound **8**: oil; R_f = 0.37 (EtOAc–CH$_2$Cl$_2$, 4:1). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 7.32–7.08 (m, 5 H, Ph), 4.19 (m, 1 H, H-2), 3.73 (s, 3 H, OCH$_3$), 3.70 (s, 3 H, OCH$_3$), 3.18–3.07 (m, A part

of an ABX system, 1 H, H-5), 2.91–2.71 (m, B part of an ABX system, 1 H, H-5), 2.69–2.43 (m, 5 H, H-3, H$_2$-3′, NHCH$_2$CH$_2$Ph), 2.41–1.81 (m, 6 H, 2 × CH$_2$COOMe, NHCH$_2$CH$_2$Ph, NH, H-4), 1.71–1.64 (m, 1 H, H-1′), 1.62–1.35 (m, 11 H, Boc, H$_2$-2′), 1.01/0.92 (m, 3 H, CHCH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.8, 27.7 (3 C), 29.6, 31.9, 35.9, 39.8, 41.4, 43.8, 44.9, 47.9, 49.7, 51.3 (2 C), 56.2, 56.7, 65.0, 78.8, 112.8, 115.9, 121.4, 132.7, 147.2, 149.4, 172.0, 171.3, 174.8. ESI-MS: C$_{28}$H$_{44}$N$_2$O$_8$ [M + H]$^+$: 537. Anal. Calcd for C$_{28}$H$_{45}$ClN$_2$O$_6$ (hydrochloride): C, 58.7; H, 7.8; Cl, 6.2; N, 4.9. Found: C, 58.5; H, 7.7; Cl, 6.0; N, 4.7.

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