Model Studies Towards Kainic Acid

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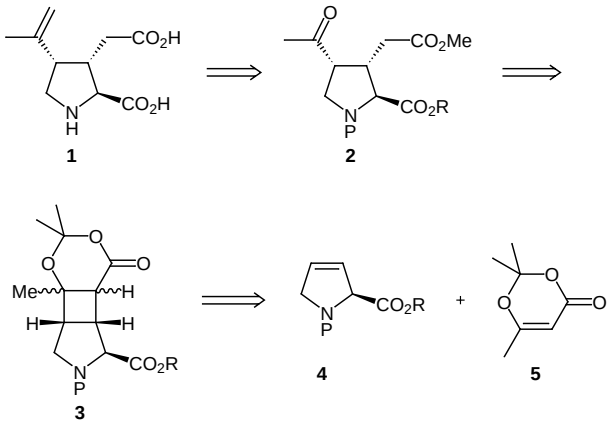
Abstract: A novel photochemical approach to the kainoid ring system is presented alongside model studies to demonstrate its feasibility.

Key words: kainic acid, photochemistry, cycloadditions, cyclobutanes, natural products

The kainoid amino acids have attracted considerable interest in the fields of biology and neurobiology due to their pronounced insecticidal, anthelmintic and, principally, neuroexcitatory properties.[1] Kainic acid 1 has demonstrated extremely potent activity on both the vertebrate and invertebrate glutaminergic systems, leading to specific neuronal death in the brain,[2] and its pronounced neuroexcitatory properties have been well documented.[3] The pharmacological effects and the patterns of neuronal degeneration observed after the injection of kainoids have been shown to mimic the symptoms of neuronal conditions such as epilepsy,[4] Alzheimer's disease and Huntington's chorea.[5] Additionally, it has been proposed that the neuronal death induced by kainoids is a good experimental model for the neuronal cell loss observed in senile dementia.[2]

Our rapid approach to the kainoid ring system is illustrated in the following retrosynthetic analysis (Scheme 1). Kainic acid **1** could be readily elucidated from the protected ketone **2**, which could be formed from the action of sodium methoxide in methanol on the cyclobutane **3**. The key cyclobutane **3** could be generated from the photochemically induced [2+2] cycloaddition of the protected proline derivative **4** and dioxinone **5**. The dioxinone **5** is commercially available and several literature procedures exist for the formation of the proline derivative **4**.[6]

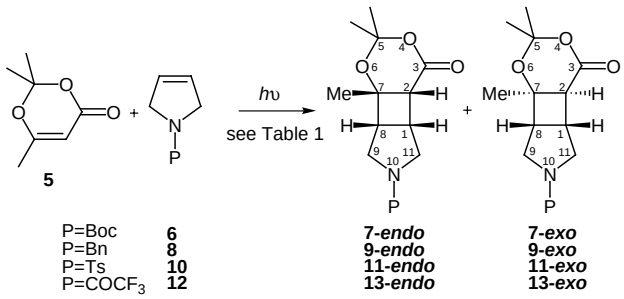
In order to evaluate the feasibility of this novel, photochemical approach a variety of model studies were conducted. Initially, the proline derivative **4** was replaced by the achiral Boc-3-pyrroline **6**, formed by a modification of the route of Meyers.[7] Irradiation of an acetonitrile solution of **6** and the photoreagent **5**, with a 125 W medium pressure mercury lamp, gave a mixture of two of the desired cyclobutanes **7**, a mixture of *endo*- and *exo*-addition products, which were readily separable by column chromatography (Scheme 2). Repeating the experiment under a



Scheme 1 Where P = protecting group, R = Me, Et, *t*-Bu etc.

variety of conditions produced an optimized combined yield of 50% (Table 1).[8]

With the success of the photocycloaddition of Boc-3-pyrroline **6**, a selection of other nitrogen protecting groups was investigated. Benzyl- (**8**) and tosyl-3-pyrroline (**10**) were generated by the action of the appropriate amine with *cis*-1,4-dichlorobut-2-ene. The trifluoroacetyl compound **12** was formed by standard protection of 3-pyrroline.[9] Submission of these protected 3-pyrrolines to the optimized photocyclization conditions gave disappointing yields for the benzyl- and tosyl-protected pyrrolines, but an increased combined yield for the trifluoroacetyl derivative (Table 2). The formation of the Boc- and trifluoroacetyl-cyclobutane systems, **7** and **13**, were repeated successfully on multi-gram scales.



Scheme 2

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Table 1

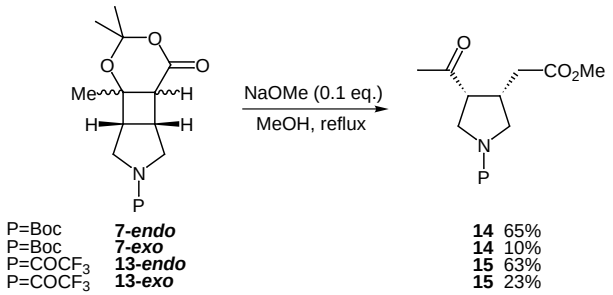
Bulb strength (W)	Solvent	Filter	Sensitizer	Time (h)	Yield of ***endo*** product (%)	Yield of *exo* product (%)
16	CH_3CN	None	None	20	17	0
125	CH_3CN	None	None	2.5	21	9
125	CH_3CN	Pyrex	Acetone	2.5	15	7
125	CH_3CN	Pyrex	None	10	0	0
125	**EtOAc**	**None**	**None**	**2.5**	**35**	**15**
400	CH_3CN	None	None	0.5	4.0	3.7
400	CH_3CN	None	None	1.0	4.2	7.6
400	CH_3CN	None	None	1.5	4.0	5.8

All photoreactions were carried out under continuous degassing with N_2, using 2 equivalents of the protected 3-pyrroline at a concentration of 0.1 mmol/mL. The yields are of isolated products after column chromatography.

Table 2

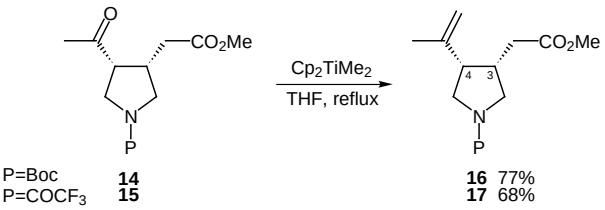
Bulb strength (W)	Solvent	Protecting group	Time (h)	Yield of *endo* product (%)	Yield of *exo* product (%)
125	EtOAc	Benzyl	2.5	0	9
125	EtOAc	Tosyl	2.5	0	0
125	**EtOAc**	**Trifluoroacetyl**	**2.5**	**47**	**12**

With reasonable quantities of the cyclobutanes **7** and **13** in hand, studies towards the methoxide induced fragmentations were conducted. A methanolic solution of the cyclobutanes **7** and **13** containing a catalytic amount of sodium methoxide was heated at reflux to yield the desired, ring-opened products **14** and **15** (Scheme 3). The *endo* compounds opened more cleanly and rapidly than their *exo* isomers, presumably due to the increased steric interactions driving the fragmentations.



Scheme 3

To complete the model studies, methylenation of the ketone functionality was examined. The use of standard Wittig methodology[10] was discounted due to the ready epimerization of the C-4 stereocenter. Consequently, the dimethyltitanocene (Cp_2TiMe_2) procedure of Petasis and Bzowej[11] was utilized. A tetrahydrofuran solution of dimethyltitanocene was readily prepared from the action of methyllithium on titanocene dichloride,[12] and refluxing this solution with the ketones **14** and **15** in the dark for 24 hours gave a good yield of the desired pyrrolidines **16** and **17**, with no observable epimerization (Scheme 4).



Scheme 4

The model studies detailed (vide supra) allow the rapid formation of the majority of the kainoid skeleton, including the crucial C-3/C-4 *cis* stereochemistry. Work in the group is now concentrating on the photocycloaddition of dioxinone **5** to a proline derivative **2** to generate a chiral, non-racemic cyclobutane, subsequent manipulation of which would afford enantiopure (–)-α-kainic acid **1**.

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(8) **A typical Procedure for the Formation of Cyclobutanes 13**:
A solution of the freshly distilled dioxinone **5** (7.10 g, 50.0 mmol)and *N*-trifluoroacetyl-3-pyrroline **12** (16.50 g, 100.0 mmol) in EtOAc (400 mL), under continuous degassing with nitrogen, was irradiated with a 125 W medium pressure mercury lamp. After 72 h TLC analysis indicated full consumption of the dioxinone. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (50% diethyl ether/petroleum ether eluent), to give two cyclobutane products.
13-endo: Colourless crystals (7.27 g, 47%); TLC, (diethyl ether) R_f = 0.20; mp 75–77 °C; IR (thin film): 2926 (s, CH_3/CH_2), 1730 (s, C^3=O), 1687 (s, N–C=O), 1157 (s, C–O) cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ = 4.46 and 4.43 (1 H, d, *J* = 12.7, 9-H), 4.32 and 4.24 (1 H, 2 × d, *J* = 12.3, 11-H), 3.52–3.20 (3 H, m, 9-H, 11-H and 1-H) 3.08 and 3.04 (1 H, 2 × dd, *J* = 9.8 and 1.9, 2-H), 2.91 and 2.84 (1 H, 2 × dd app 2 × t, *J* = 8.3, 8-H), 1.63 and 1.62 (3 H, 2 × s, 7-Me), 1.56 and 1.55 (6 H, 2 × s, 5-Me);^{13}C NMR (75 MHz; $CDCl_3$): δ = 165.9 and 165.6 (C-3), 155.4 (q, *J* = 37.4, **C**OCF_3), 115.9 (q, *J* = 300.6, CO**C**F_3), 103.8 and 103.4 (C-5), 69.5 and 69.4 (C-7), 47.7 (C-8), 46.2 and 45.8 (C-9 or C-11), 44.6 (C-8), 44.5 (C-9 or C-11), 43.5 (C-9 or C-11), 39.0 and 38.8 (C-2), 34.6 and 32.1 (C-1), 27.0, 26.9, 26.8 and 26.4 (5-Me and 7-Me);MS (EI): *m/z* (%) = 308(39) [M + H], 292(8) [M–Me], 250(77) [M–$CO(CH_3)_2$], 222(25) [M–$CO_2(CH_3)_3$], 165(83) [M–dioxinone], 143(87) [dioxinone], 85(95), 43(100) [$CH(CH_3)_2$]; HRMS (EI) found: 308.1127, [M + H], $C_{13}H_{17}NO_4F_3$ requires 308.1110.
13-exo: Colourless crystals (1.80 g, 12%); TLC, (Et_2O) R_f = 0.47; mp 99–103 °C; IR (thin film): 2924 (s, CH_3/CH_2), 2854 (s, CH), 1735 (s, C^3=O), 1689 (s, N–C=O), 1463 (s, CH_3/CH_2), 1385 and 1354 (s, $C(CH_3)_3$)cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ = 4.25 and 4.05 (1 H, 2 × d, *J* = 14.0, 9-Hu), 4.08–3.98 (1 H, m, 11-H), 3.72–3.47 (2 H, m, 9-H_d and 11-H), 3.29–3.00 (2 H, m, 1-H and 8-H), 2.71 and 2.62 (1 H, 2 × d, *J* = 3.4, 2-H), 1.67–1.61 (6 H, m, 5-Me), 1.45 and 1.39 (3 H, 2 × s, 7-Me); ^{13}C NMR (75 MHz; $CDCl_3$): δ = 170.0 (C-3), 155.4 (q, *J* = 36.7, **C**OCF_3), 116.0 (q, *J* = 287.3, CO**C**F_3), 106.73 and 106.67 (C-5), 76.0 (C-7), 53.1 and 52.0 (C-11), 47.6 and 47.3 (C-9), 46.9 and 46.8 (C-8), 45.1 and 44.6 (C-2), 40.3 and 44.6 (C-1), 27.0, 29.6, 29.1 and 28.9 (5-Me), 22.0 and 21.7 (7-Me); MS (EI): *m/z* (%) = 308(12) [M + H], 292(5) [M–Me], 250(52) [M–$CO(CH_3)_2$], 165(80) [M–dioxinone], 143(87) [dioxinone], 69(62) [CF_3], 59(49) [$(CH_3)_2CHO$] 43(100) [$CH(CH_3)_2$]; HRMS (EI) found: 308.1128, [M + H], $C_{13}H_{17}NO_4F_3$ requires 308.1110.

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