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A Total Synthesis of (-)-α-Kainic Acid By the Pauson-Khand Reaction

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Abstract: A total synthetic route to (-)-α-kainic acid has been developed based on the Pauson-Khand reaction as a key reaction for the construction of the bicyclo ring system.

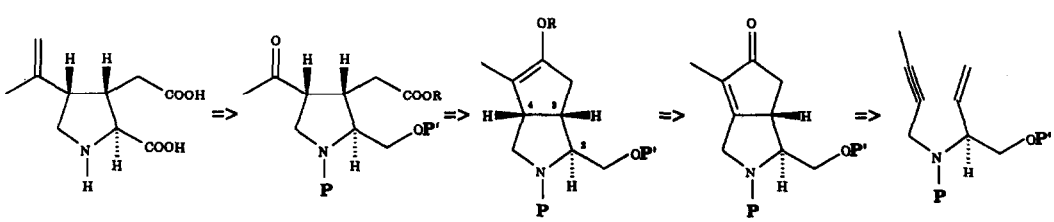
The unique structure and novel biological activities (anthelmintic[1], insecticidal[2] and neuroexitatory activity[3]) of kainic acid **1**, isolated from the marine algae *Digenea Simplex*[4], had led to the development of several interesting synthetic strategies[5].

In this paper we would like to describe our continuing endeavor[6] toward the total synthesis of optically active α-kainic acid based on the Pauson-Khand reaction. Dealing with a synthetic scheme for α-kainic acid, one should address the problems of not only building up necessary side chains but also controlling the stereochemistry at C2, C3 and C4 positions.

Retrosynthetic analysis (Scheme 1) of kainic acid suggested that the ketone **2**, which can be readily transformed into **1**, should, in principle, be derivable by the oxidative cleavage of the enolether **3**. The enolether **3** would be obtained by trapping the enolate generated by the 1,4-reduction of the enone **4**. The most important aspect in the scheme for controlling the stereochemistry at C3 and C4 positions lies in the fact that the reduction would proceed to form only the cis fused bicyclo[3.3.0]octane system due to the nature of the ring system. Furthermore, the trans stereochemistry between C2 and C3 positions would be realized during the Pauson-Khand reaction[7].

Starting with an optically active vinylglycine derivative **6**[8], the ene-yne **10** was prepared according to Scheme 2. The ester **6** was reduced to **7** with $LiBH_4$ and the hydroxyl group was

Scheme 1

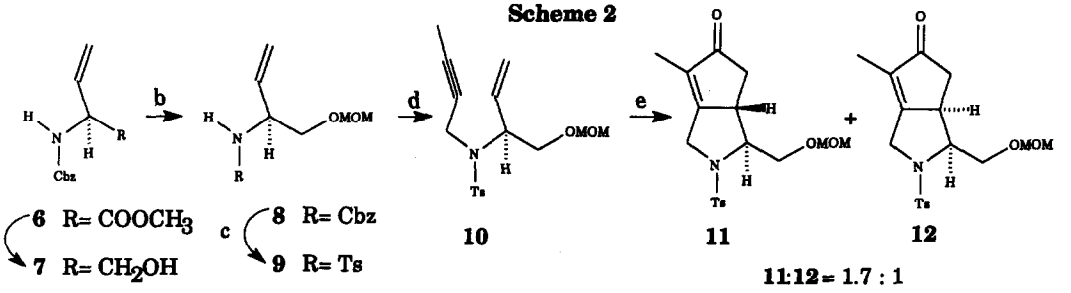


1 **2** **3** **4** **5**

P, P': protecting groups

protected with a methoxymethyl (MOM) group. In order to perform further chemical transformations, the Cbz group of **8** was replaced with the Ts group by the following sequence of reactions: (i) Li/NH_3,THF, (ii) $TsCl/Na_2CO_3$. The *N*-alkylation of **9** was accomplished with 3-methyl-2-butyn-1-ol mesylate to give the key intermediate **10**.

Scheme 2



a) $LiBH_4$ / MeOH, 0 °C, 87% b) MOMBr, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, room temp., 93%

c) Li / NH_2 - THF, -33 °C and then TsCl, Na_2CO_3, room temp., 65%

d)  ,NaH / DMF, room temp., 88%

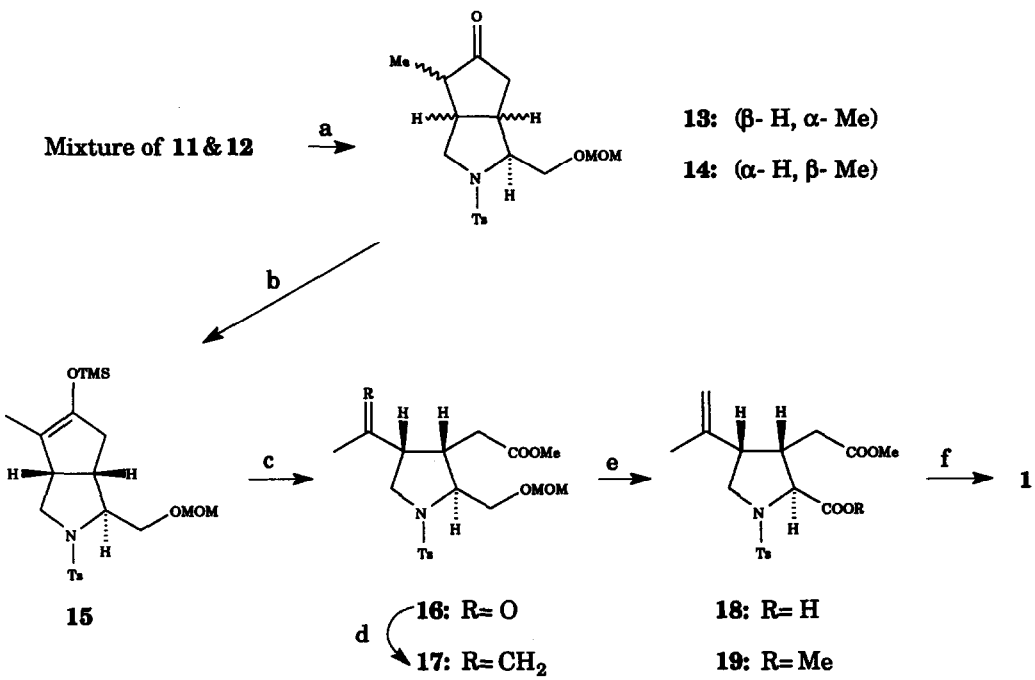
e) $Co_2(CO)_8$ / CH_2Cl_2 and then MNO or TMANO, 95%

When the ene-yne **10** was subjected to the Pauson-Khand reaction condition [(i) $Co_2(CO)_8$, CH_2Cl_2, room temp., (ii) trimethylamine *N*-oxide (TMANO)[9] or 4-methylmorpholine *N*-oxide (MNO)[10]], the reaction proceeded smoothly to give an inseparable mixture of two diastereoisomers, **11** and **12** (1.7:1 ratio) in 95% yield. The major isomer to possess desired stereochemistry as depicted was ascertained by converting it into α-kainic acid.

The transformation of **11** to **1** is shown in Scheme 3. Hydrogenation of the mixture of enones (**11** and **12**) gave a mixture of ketones (**13** and **14**) which were separable by silica gel column chromatography[11]. Treatment of the major isomer **13** using Holton's method[12] gave a thermodynamically more stable enolether **15** in a regioselective manner (97:3 ratio). The ketoester **16** was prepared from **15** by ozonolysis followed by esterification with diazomethane. The Wittig reaction of **16** proceeded smoothly to give **17**[13] without epimerization at C4 position[14]. A MOM group on **19** was then deprotected with trifluoroacetic acid and the resulting alcohol was oxidized to acid **18** with PDC.

In order to purify the oxidation product, esterification of the crude acid **18** and purification with a column chromatography on SiO_2 gave pure **19**. The diester **19** was then hydrolyzed and the tosyl group of the resulting diacid was removed by a dissolving metal reduction to give **1**. Finally, treatment of the reaction mixture with a weakly acidic ion exchange resin (Amberlite CG50) and crystallization (in ethanol) afforded optically pure α-kainic acid ($[\alpha]_D^{20}$ = -14.7° (c=1.5, H_2O)] which was identical to the natural kainic acid as confirmed by ^1H-NMR (300MHz).

Scheme 3



a) H_2 (1 atm), Pd/C, EtOAc, 98% (**13** + **14**) b) $FeCl_3$, EtMgBr, TMSCl, Et_2O-THF, room temp., 95%

c) (i) O_3 (ii) $(CH_3)_2S$ (iii) CH_2N_2, 90% d) $Ph_3P{=}CH_2$, THF, 0 °C, 72%

e) (i) CF_3COOH, CH_2Cl_2, room temp. (ii) PDC, DMF, room temp. (iii) CH_2N_2, 78%

f) (i) LiOH, MeOH - H_2O, room temp. (ii) Li / NH_3 - THF, -78 °C, 87%

References and Notes

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11) NMR data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83(dd,1H), 1.00(d,3H), 2.35(m,2H), 2.45(s,3H), 2.64(t,1H), 2.74(m,1H), 3.17(m,1H), 3.38)s,3H), 3.62(m,3H), 3.84(m,1H), 4.67(d,2H), 7.34(d,2H), 7.72(d,2H)
NMR data for **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96(d,3H), 1.50(m,1H), 1.72(m,1H), 2.34(dd,1H), 2.44(s,3H), 2.47(m,1H), 2.91(m,1H), 3.19(dd,1H), 3.37(s,3H), 3.63(m,1H), 3.74(m,2H), 3.87(dd,1H), 4.63(dd,2H), 7.33(d,2H), 7.72(d,2H)
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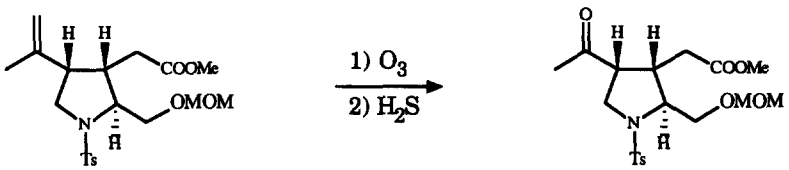
13) NMR data for **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95(dd,1H), 1.67(s,3H), 1.79(dd,1H), 2.45(s,3H), 2.66(m,1H), 3.05(m,2H), 3.39(s,3H), 3.52(dd, 1H), 3.59(s,3H), 3.67(m,2H), 3.79(dd,1H), 4.52(s,1H), 4.66(dd,2H), 4.86(d,1H), 7.35(d,2H), 7.76(d,2H)
^{13}C NMR (75.469 MHz, $CDCl_3$) ppm 21.5, 22.7, 31.9, 39.1, 45.1, 48.8, 51.5, 55.3, 64.3, 70.1,96.5, 112.2, 127.5, 129.6, 133.2, 140.5, 143.7, 172.3
14) In order to confirm no epimerization at C4 during the Wittig reaction, the tosylate **17** was reconverted to **16** by ozonolysis and the product was identical to the starting material **16** by NMR.



17 **16**

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