A SHORT AND EFFICIENT STEREOSELECTIVE SYNTHESIS OF α-ALLOKAINIC ACID[1].

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α-Allokainic acid and α-kainic acid, isolated from the marine algae Digenea simplex Ag.[2], have been assigned structures 1 and 2 on the basis of chemical[3] and X-ray evidence[4]. Both amino acids show antihelmintic properties and more recently, acquired further medicinal interest, due to their neurophysiological activity in mammals[5].

1

α-ALLOKAINIC ACID

2

α-KAINIC ACID
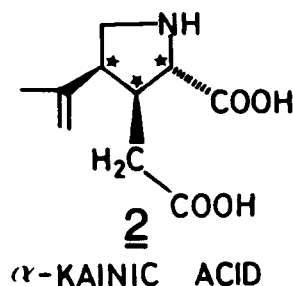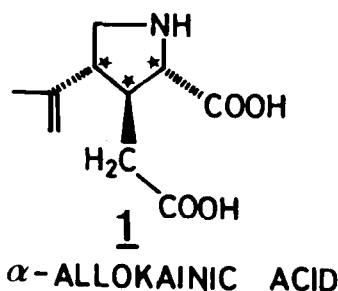
Early synthetic work resulted in several multistep routes to 1, proceeding in low overall yield[6]. In extension of our systematic studies of intramolecular ene reactions[7] we now have accomplished the following, different approach to 1.

Starting from the easily accessible N-trifluoroacetylaminomalonic ester 3[8] N-alkylation (NaH(1 equiv.)/1-bromo-3-methyl-1-butene[9] (1,3 equiv.)/HMPT/ 25°/24h/N_2) furnished the 1,6-diene 4[10] (m.p. 48 - 49°C) in 80% yield. Cyclisation of the diene 4 proceeded at surprisingly low temperature (5% solution in toluene/25°C/3 months or 80°C/24 h) or, more conveniently, on heating

neat 4 in a bulb tube to 170°C for 10 min at 1 Torr to give after distillation

at 150°C/0,05 Torr exclusively the trans-substituted pyrrolidine 5[10] in 97%

yield. Whether or not the observed stereoselectivity of the crucial ene reaction

4 → 5 is due to kinetic or thermodynamic control remains to be clarified[11].

Concomitant hydrolysis of the ester and amide groups in 5, followed by decarbo-

xylation was achieved by heating 5 at reflux with 0,5 N NaOH in MeOH/H_2O(1:1)

and subsequent slow acidification of the boiling solution with 2N aqu. HCl to

p_H= 3[12]; addition of Cu(OAc)$_2$, filtration of the precipitated copper salt

(78% yield) and its decomposition with H_2S in water furnished (±)-α-allokainic

acid 1 (m.p. 245 - 250°C (decomp.) 88% yield) as the only stereoisomer[12].

Crystallisation of its (-)-ephedrine salt[6a] afforded the enantiomerically

pure (+)-1 (m.p. 238 - 242°C (decomp.) $[\alpha]_D^{20}$= +7,7° (c=1,3, H_2O)) identical

with natural 1 as shown by IR, ^{1}H-NMR (100 MHz), chiroptic and mixed m.p.

evidence.
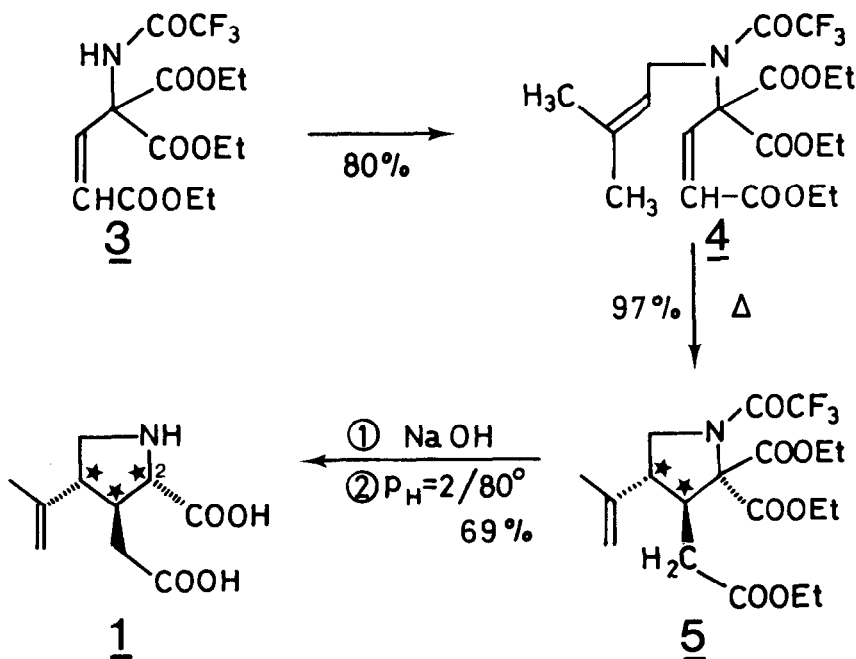
In summary, this route leads to $(\overset{+}{-})$-α-allokainic acid ($\underline{1}$) from $\underline{3}$ in 53% overall yield, nicely illustrating the preparative potential of intramolecular ene reactions. A related stereocontrolled synthesis of α-kainic acid $\underline{2}$ is presently under study in our laboratory.

REFERENCES

1) Reported by one of us (W.O.) at the Chemische Gesellschaft Zürich on Dec. 7, 1977.

2) S. Murakami, T. Takemoto and Z. Shimizu, J. Pharm. Soc. Japan, $\underline{73}$, 1026 (1953); H. Morimoto, ibid. $\underline{75}$, 937 (1955); S. Murakami, T. Takemoto, Z. Tei, K. Daigo and N. Takagi, ibid. $\underline{75}$, 1252 (1955).

3) M. Miyasaki, J. Pharm. Soc. Japan, $\underline{75}$, 695 (1955); Y. Ueno, H. Nawa, J. Ueyanagi, H. Morimoto, R. Nakamori and T. Matsuoka, ibid. $\underline{75}$, 807 (1955).

4) H. Watase, and I. Nitta, Bull. chem. Soc. Japan $\underline{30}$, 889 (1957); H. Watase, Y. Tomic and I. Nitta, ibid. $\underline{31}$, 714 (1958); Nature $\underline{181}$, 761 (1958).

5) T.J. Biscoe, R.H. Evans, P.M. Headly, M. Martin and J.C. Watkins, Nature $\underline{255}$, 166 (1975); E.G. McGeer and P.L. McGeer, ibid., $\underline{263}$, 517 (1976).

6)a) M. Miyamoto, T. Sugawa, H. Morimoto, M. Uchibayashi, T. Tanaka and S. Tatsuoka, J. Pharm. Soc. Japan $\underline{77}$, 580 (1957); b) M. Miyamoto, M. Honjo, Y. Sanno, M. Uchibayashi, K. Tanaka and S. Tatsuoka, ibid. $\underline{77}$, 586 (1957); c) M. Honjo, ibid., $\underline{77}$, 598 (1957); d) T. Sugawa, ibid., $\underline{78}$, 867 (1958);

e) M. Honjo, ibid., 78, 888 (1958); f) K. Tanaka, M. Miyamoto, M. Honjo,

H. Morimoto, T. Sugawa, M. Uchibayashi, Y. Sanno and S. Tatsuoka, Proc.

Japan. Acad. 33, 47 (1957).

7)a) W. Oppolzer, E. Pfenninger and K. Keller, Helv. 56, 1807 (1973); b) W.

Oppolzer, K.K. Mahalanabis and K. Bättig, Helv. 60, 2388 (1977); c) Review

W. Oppolzer and V. Snieckus, Angew. Chem., in press.

8) Y. Kishida and A. Tereda, Chem. Pharm. Bull. 17, 2417 (1969).

9) H.L. Simon, A. Kaufmann and H. Schinz, Helv. 29, 1133 (1946).

10) IR, ^{1}H-NMR and mass spectra are in full agreement with the assigned

structure.

11) For the counterplay of kinetic versus thermodynamic stereocontrol in

intramolecular ene reactions see ref. 7c.

12) CO_2-evolution starts already at p_H=6. The stereoselectivity of the trans-

formation 5 → 1 is apparently kinetically controlled since 1 does not

incorporate deuterium at C(2) on treatment with NaOD in boiling MeOD/D_2O

followed by acidification with CF_3COOD to p_H=2,5. It seems possible that

this steric control arises from intramolecular protonation of the decarbo-

xylated enol intermediate at C(2) by the acetic acid side chain.