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A SHORT AND STEREOSELECTIVE SYNTHESIS OF PERHYDROHISTRIONICOTOXIN

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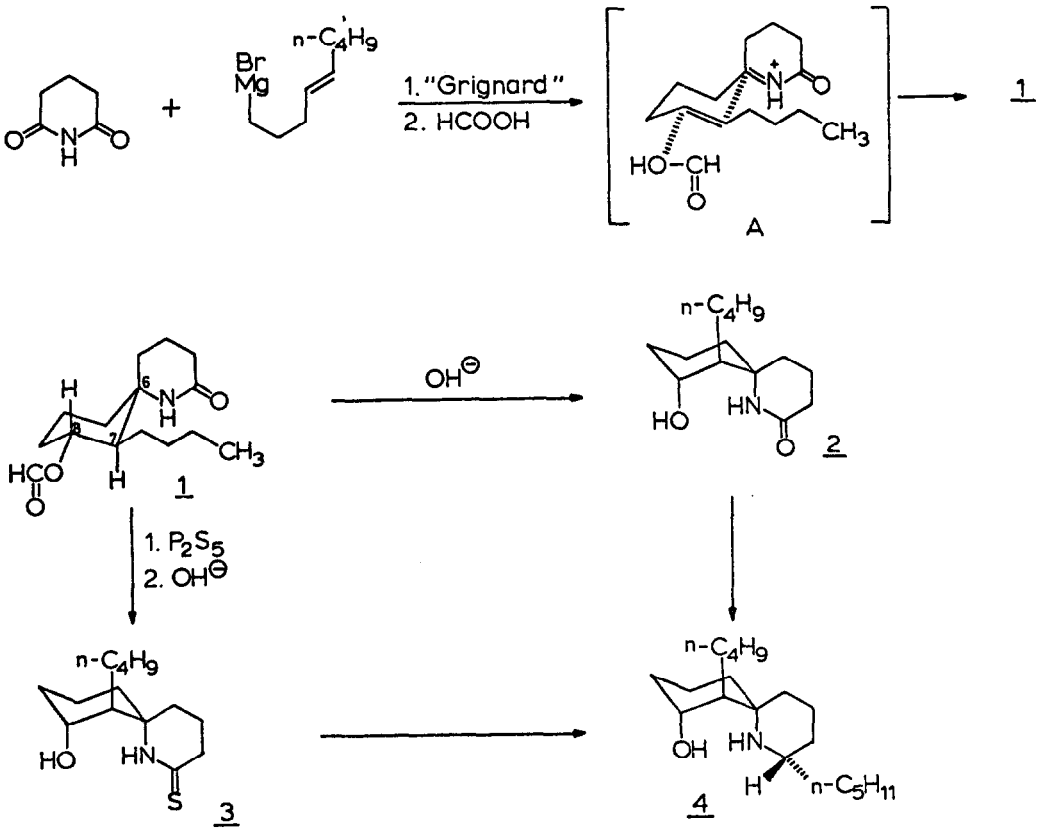
Histrionicotoxin[1] and its congeners are used in studies concerning the mechanisms involved in the transsynaptic transmission of neuromuscular impulses. Perhydrohistrionicotoxin shows a similar behaviour and has been shown[2] to bind selectively to that part of the cholinergic receptor that regulates the ion transport mechanisms (ion conductance modulator) without affecting the binding of acetylcholine to the receptor. In connection with this remarkable biological activity a general and stereoselective synthesis of perhydrohistrionicotoxin and similar compounds seem to be of high interest. Recently total syntheses were reported by Kishi et al.[3] and Corey et al.[4]

The keystep of our synthesis of perhydrohistrionicotoxin in which three asymmetric centra are formed simultaneously involves the reaction of glutarimide with (E)-4-nonene-1-ylmagnesium bromide[5] followed ("one pot"-reaction) by a stereoselective α-acyliminium ion initiated olefin cyclisation[6]. Based upon considerations of molecular models and abundant experiences in heterocyclisation[7] a preference for transition state A is envisaged in the reaction of the (E)-olefin in which eventually will lead to a product with the right relative stereochemical configurations at the carbon atoms C_6, C_7 and C_8.

Thus reaction of 1 eq of N-H glutarimide with 2.2 eq of (E)-4-nonene-1-ylmagnesium bromide in THF (30-35°, 18 hr) followed by evaporation of the solvent and cyclisation of the residue in HCOOH (44°, 8 days) gave after column chromatography (SiO_2, act II, EtOAc) and recrystallisation from isopropylether the crystalline formate ester 1 (m.p. 144-146°) in 23% yield[8]. IR($CHCl_3$): 1720 cm^{-1} (CO ester); 1640 cm^{-1} (CO lactam); 3390 cm^{-1} (N-H). ^1H NMR δ(C_6D_6): 8.40 (br s,

1H, N-H), 7.68 (s, 1H, HCOO) 4,65-5.00 (t of d, 1H, H_8ax) 0.80-2.40 (m, 22H). ^{13}C NMR δ($CDCl_3$): 171.9 (s, N-C=O), 160.1 (d, HC=O), 58.5(S, spiro C_6). Only traces of other isomers could be detected.



The formate ester 1 could be hydrolysed (KOH-EtOH-H_2O) to the crystalline hydroxy spirocompound 2[9] (m.p. 135-136°). IR(KBr): 1640 cm^{-1} (CO lactam). ^1H NMR δ($CDCl_3$): 8.55 (br s, 1H, NH), 5.23 (br d, 1H, OH), 4.05 ($W_{½}$=8 Hz, 1H, H_8 eq), 0.88 (br t, 3H, CH_3), 1.1-2.5 (m, 19 H). ^{13}C NMR δ($CDCl_3$): 69.9 (d, C-OH), 57.5 (s, spiro C_6). Reaction of 1 with P_2S_5 in refluxing benzene[3], followed by hydrolysis yielded (89%) the crystalline thiolactam[9] 3 (m.p. 162-165°). IR($CHCl_3$): 1520 cm^{-1} (NH-C=S); ^1H NMR δ($CDCl_3$): 4.07 (m, 1H, H_8eq); 2.5-3.2 (m, 2H). 1.00-2.2 (18H); 0.90 (br t, 3H, CH_3). From the 300 MHz spectrum of 1 taken in C_6D_6 the trans diequatorial relationship between the formate substituent and

the n-butylgroup could be established unambiguously (J_1=10.5 Hz, J_2= 10.5 Hz, J_3=4.5 Hz).

Furthermore NOE experiments on 1 suggested the trans relationship between the C-N bond and the n-butyl group (irradiation of the N-H proton resulted in an increase of the integral for H_7ax).

The hydroxy spirocompound 2 was shown to possess an axial OH-substituent ($W_{\frac{1}{2}}$=8 Hz for H_8eq) due to internal H-bonding with the amide function, thus establishing the cis-relationship between the OH-substituent and the C-N bond. Compound 3 also possesses an axial OH substituent.

Since 3 has been converted to perhydrohistrionicotoxin (4) in 70% yield[3], the stereoselective synthesis of 1 and its conversion to the thiolactam 3 formally constitute a new total synthesis of perhydrohistrionicotoxin.

This short and stereoselective synthesis of the perhydrohistrionicotoxin precursor 1 accentuates the potential of α-acyliminium ion initiated olefin cyclisations in the total synthesis of this type of compounds. The possibility to modify both the heterocyclic and the olefinic synthons offers a method for the stereocontrolled construction of a host of 1-aza-spiranes, functionalized both in the heterocyclic and carbocyclic rings. Thus a similar reaction of (Z)-4-nonene-1-ylmagnesium bromide and glutarimide afforded the C_7-epimer of 1 in 22% yield[10].

Stereocontrolled syntheses of other 1-aza-spiranes by the α-acyliminium methodology are under active investigation.

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References

1. T. Tokuyama, K. Uenoyama, G. Brown, J.W. Daly and B. Witkop, Helv. Chim.Acta, 57, 2597 (1974).
2. E.X. Albuquerque, K. Kuba and J.W. Daly, J.Pharmacol.Exp.Therap., 189, 513 (1974).
3a. M. Aratani, L.V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inoue, J.Org.Chem., 40, 2009 (1975);
b. T. Fukuyama, L.V. Dunkerton, M. Aratani and Y. Kishi, J.Org.Chem., 40, 2011 (1975).
4a. E.J. Corey, J.F. Arnett and G.N. Widiger, J.Am.Chem.Soc., 97, 430 (1975);
b. E.J. Corey, M. Petrzilka and Y. Ueda, Helv.Chim.Acta, 60, 2294 (1977);
c. E.J. Corey and R.D. Balanson, Heterocycles, 5, 445 (1976).
5. G. Ohloff, C. Vial, F. Näf and M. Pawlak, Helv.Chim.Acta, 60, 1161 (1977).
6. H.E. Schoemaker and W.N. Speckamp, Tetrahedron Lett., 1515 (1978).
7. H.E. Schoemaker, J. Dijkink and W.N. Speckamp, Tetrahedron, 34, 163 (1978).
8. Not optimized.
9. The spectral data (IR, NMR, Mass spectrum) of compounds 2 and 3 could be compared with the original spectra kindly provided by Prof. Y. Kishi. Compound 2 was identical in all respects with an authentic sample also provided by Prof. Y. Kishi.
10. To be published separately.

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