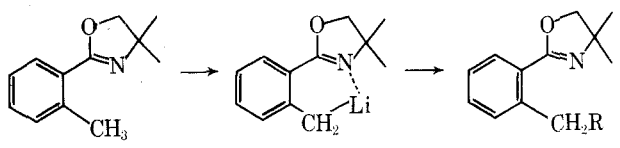


10 11 12, 13 (see Table II)

One of the attractive and useful aspects of this new method of ortho-lithiation is the possibility for further modifications and transformations of the oxazoline group under mild conditions: (i) into ketones *via* N-alkylation and addition of an organometallic reagent,[12] (ii) into aldehydes by reduction,[13,14] (iii) into ester or acids by solvolysis.[5]

Acknowledgment. We wish to acknowledge the support and encouragement of Dr. Neville Finch and the carefully executed work of Ms. Ruth Behnke (NMR), Mrs. Barbara Warren (MS), and Mr. Stuart Brody (GC, midrodistillations).

Supplementary Material Available. Full experimental details and analytical data on compounds **3–9** and **12, 13** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy, or $2.50 for microfiche referring to code number JOC-75-2008.

References and Notes

(1) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 475 (1969).
(2) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).
(3) H. R. Rodriguez, private communication.
(4) Our own unpublished results.
(5) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
(6) P. Allen and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).
(7) H. Gilman, *Org. React.*, **8**, 258 (1954).
(8) Ketones and aldehydes react, of course, equally well with **2**. However, because of the propensity of internal nucleophilic attack of the OH group at the trigonal oxazoline carbon, the primary product is usually obtained as a mixture and thus better carried on to the corresponding phthalides as described by Meyers.[5]
(9) R. L. Vaux, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).
(10) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 83 (1969).
(11) P. L. Creger, *J. Am. Chem. Soc.*, **92**, 1396 (1970).
(12) A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972).
(13) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(14) I. C. Nordin, *J. Heterocycl. Chem.*, **3**, 531 (1966).

Research Department **Heinz W. Gschwend***
Pharmaceuticals Division **Ali Hamdan**
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Received April 15, 1975

Synthetic Studies on Histrionicotoxins. I. A Stereocontrolled Synthesis of (±)-Perhydrohistrionicotoxin

Summary: A stereocontrolled synthesis of (±)-perhydrohistrionicotoxin (**18**) was achieved by using a reaction of acylaziridine **11** with dibutylcopper lithium as a key step.

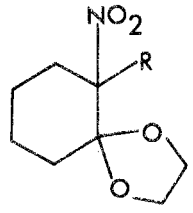
Sir: Histrionicotoxins,[1] the toxic principles isolated from the venom of the Columbian frog *Dendrobates histrionicus*, are remarkably useful neurophysiological tools which selectively inhibit the ion transport mechanism of the cholinergic receptor.[2] Recent communication[3] on a synthesis of perhydrohistrionicotoxin prompted us to report our synthetic studies in this field.

The spiro ketolactam **4** was synthesized by the following simple procedures in 60% overall yield from **1**. Treatment of 2-nitrocyclohexanone ketal[4,5] **1** [bp 125–127° (7mmHg)] with methyl acrylate in *tert*-butyl alcohol containing Triton B, followed by hydrolysis (NaOH in aqueous methyl alcohol at room temperature), afforded the nitro acid[5] **2** (mp 130–131°). The nitro acid **2** was homologated to the nitro ester[5] **3** (oil) by Arndt–Eistert reactions, i.e., (1) $SOCl_2$ in C_6H_6 at 50°, (2) CH_2N_2 in Et_2O at room temperature, (3) $AgBF_4$–Et_3N in methyl alcohol at 0°. Catalytic hydrogenation of **3** (Raney Ni in methyl alcohol at 50°), followed by deketallization (aqueous TFA at 75°), afforded the spiro ketolactam[5] **4** (mp 150–152°).

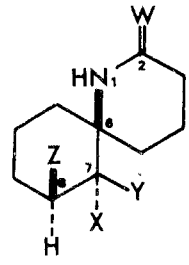
A possibility to control the stereochemistry at the 6 and 7 positions was first examined. Namely, sodium borohydride reduction of **4** in methyl alcohol gave in 85% yield the alcohol[5] **5** (mp 160–162°), which was converted to the mesylate[5] **6** (mp 157–158°). The stereochemistry of the alcohol **5** was assigned based on the fact that sodium hydride treatment of **6** in wet THF yielded cleanly the acylaziridine[5] **7** (oil). Acetic acid treatment of **7** gave exclusively the acetate[5] **8** (mp 143–144°),[6] identical with the acetate obtained by acetylation of the alcohol **5**. This acetolysis result suggested that the required functionality with the desired stereochemistry could be introduced by opening the acylaziridine system in **7**. Thus, **7** was allowed to react with dibutylcopper lithium in THF at room temperature, to give exclusively the lactam **9** (oil) in ~65% yield.[5,6] On the other hand, butyllithium or butylmagnesium bromide reacted with **7** in a 1,2-addition fashion.[7]

In order to apply the described method to the real synthesis, the mesylate[5] **10** (melting point of the corresponding alcohol, i.e., X = OH in **10**, 134–135°) was stereospecifically synthesized from **4** in 35% overall yield by six successive operations [(1) $(EtO)_3CH$–H^+, (2) Δ,[8] (3) Br_2, (4) $NaBH_4$,[9] (5) *i*-PrONa–*i*-PrOH,[10] (6) MsCl–Py]. Sodium hydride treatment of **10** in wet benzene at room temperature yielded cleanly the acylaziridine[5] **11** (oil), which was allowed to react with dibutylcopper lithium in THF at room temperature to afford the lactam[5] **12** (oil) in 15% yield from **10**. One of the undesired products (~30%) in this reaction was the olefin[5] **13** (mp 115–117°); **13** was possibly derived from the halo intermediate **14**.[7]

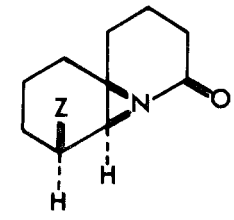
The lactam **12** was converted to the thiolactam[5] **15** (melting point unrecorded) by P_2S_5 in refluxing benzene. The thiolactam **15** was converted to the imine[5] **16** (oil) by two steps, i.e., thioimino ether formation with Meerwein reagent and alkylation with pentyllithium in hexane–ether containing diisobutylaluminum hydride. In the last alkylation process, the activation of the carbon–nitrogen double bond and solvent system are critical.[11] Boron tribromide treatment of **16** in methylene chloride (i.e., **16** → **17**), followed by aluminum hydride reduction in cyclohexane, afforded a mixture of (±)-perhydrohistrionicotoxin (**18**) [six parts, melting point (in a sealed tube) as its hydrochloride, 159–161°] and (±)-*epi*-perhydrohistrionicotoxin (**19**) [one part, melting point (in a sealed tube) as its hydrochloride, 199–201°], which could be separated by preparative TLC or by direct crystallization and recrystallization as the hydrochloride. Stereochemistry of the aluminum hydride reduction is obviously controlled by a complex formation of the reducing reagent with the alcoholic function in **17**, because aluminum hydride reduction of **16** in THF or sodium borohydride reduction of **17** in methyl alcohol gave the



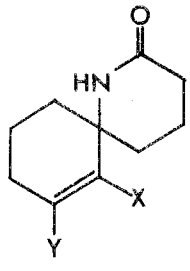
1 R=H
2 R=$(CH_2)_2CO_2H$
3 R=$(CH_2)_3CO_2CH_3$



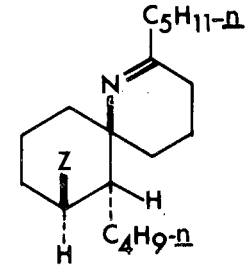
4 X,Y=O, Z=H, W=O
5 X=OH, Y=H, Z=H, W=O
6 X=OMs, Y=H, Z=H, W=O
8 X=OAc, Y=H, Z=H, W=O
9 X=n-Bu, Y=H, Z=H, W=O
10 X=OMs, Y=H, Z=OPr^i, W=O
12 X=n-Bu, Y=H, Z=OPr^i, W=O
14 X=hal, Y=H, Z=OPr^i, W=O
15 X=n-Bu, Y=H, Z=OPr^i, W=S
20 X=n-Bu, Y=H, Z=OH, W=O



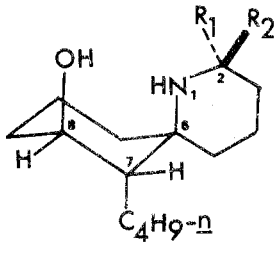
7 Z=H
11 Z=OPr^i



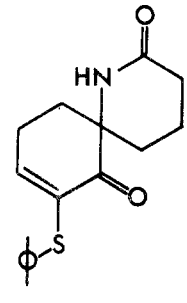
13 X=Y=H
21 X=OEt, Y=H



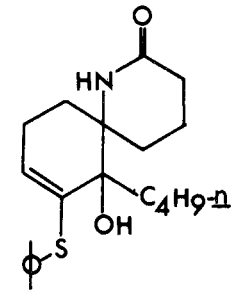
16 Z=OPr^i
17 Z=OH



18 R_1=n-C_5H_{11}, R_2=H
19 R_1=H, R_2=n-C_5H_{11}



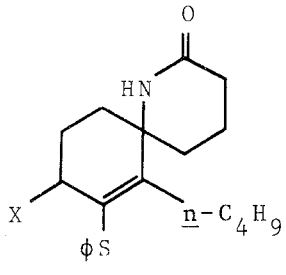
22



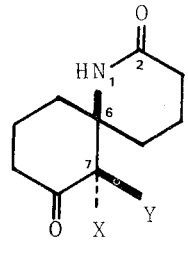
23

product belonging to the epi series as the major product. The best overall yield from the lactam **12** to (±)-perhydrohistrionicotoxin (**18**) was ~55%. Synthetic perhydrohistrionicotoxin (**18**) [melting point (in a sealed tube) as its hydrochloride, 159–161°] was identical with the authentic substance[12] by comparison of spectroscopic data (MS, NMR, ir), chromatographic behavior (silca gel and aluminum oxide TLC), and physiological activity.[13]

For the practical purposes, a more efficient route to the spiro lactam alcohol **20** was sought. Phenylsulfenyl chloride treatment of the enol ether[5,8] **21** (mp 126–127°) in methylene chloride gave thiophenylenone[5] **22** (mp 170–171°), which reacted with butylmagnesium chloride in THF to give the carbinol[5] **23** (mp 201–202°) in 80% overall yield. Thionyl chloride treatment of **23** gave the chloride[5] **24** (oil), which was reduced to the thiophenylenol[5] **25** (oil) with zinc–hydrogen chloride. Hydrolysis of **25** with concentrated hydrobromic acid yielded a mixture of the epimeric spiro ketolactams[5,14] **26** (one part) and **27** (three parts).[15] Equilibration of the mixture of **26** and **27** in methylene chloride containing sodium methoxide gave a new mixture composed of four parts **27** and one part **26**. Lithium or calcium ammonia reduction[16] of **27** at −78° gave exclusively the desired alcohol[5] **20** (mp 133–134°), which was identified with the authentic alcohol synthesized by hydrolysis of **12** (BBr_3 in CH_2Cl_2). Conventionally, the equilibrated mixture of **26** and **27** was subjected to the lithium or calcium reduction and the desired alcohol **20** was easily isolated in 50% yield by a short silica gel column chromatography. The fraction containing the undesired alcohols (epimers at the 7 position) could be recycled by Jones oxidation, equilibration,



24 X=Cl
25 X=H



26 X=H, Y=n-C_4H_9
27 X=n-C_4H_9, Y=H

and reduction. The overall yield from the spiro ketolactam **4** to the alcohol **29** was ~20% (the conditions have *not* been optimized; the recycle procedure is *not* counted).

The alcohol **20** could be converted to (±)-perhydrohistrionicotoxin (**18**) in ~65% overall yield by following the method established before.[17,18]

Supplementary Material Available. Experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfilm (105 × 148mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W. Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfilm, referring to code number JOC-75-2009.

References and Footnotes

(1) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, *Helv. Chim. Acta*, **57**, 2597 (1974), and references therein.
(2) E. X. Albuquerque, K. Kuba, A. J. Lapa, J. W. Daly, and B. Witkop, *Excerpta Med. Found. Int. Congr. Ser. n333*, 585 (1973), and references therein.
(3) E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, **97**, 430 (1975).
(4) The ketal **1** was synthesized from 2-nitrocyclohexanone [C. Bischoff and E. Schröder, *J. Prakt. Chem.*, **314**, 891 (1972)].
(5) Satisfactory spectroscopic data (MS, NMR, ir, and uv) were obtained on this compound.
(6) The precise yield could not be obtained on this reaction because of the high volatility of **7**.
(7) Detailed results on the reaction of acylaziridine with dialkylcopper lithium and with alkyllithium and Grignard reagents will be reported elsewhere.
(8) Product at this stage is the enol ether[5] **21**.
(9) Product at this stage is the bromohydrin[5] (mp 156–158°; i.e., X = OH, Y = H, Z = Br, and W = O in structure **5**), which yield "α" epoxide upon basic treatment.
(10) Stereochemistry of the mesylate **10** is controlled by opening "α" epoxide by isopropoxide. Epoxidation of the olefin **13** with *m*-chloroperbenzoic acid gave "β" epoxide as the major product, which is opened again at the 8 position by isopropoxide; dibutylcopper lithium opened the "β" epoxide also at the 8 position.
(11) We had studied independently a method converting **12** into perhydrohistrionicotoxin similar to the reported method,[3] but the results were less satisfactory than the present method.
(12) Generously supplied by Dr. B. Witkop and Dr. T. Tokuyama.
(13) Kindly carried out by Professor E. X. Albuquerque.
(14) The ratio (**26**:**27**) depends on the acidic work-up conditions. Sterochemical assignments of **26** and **27** were made on the basis that **27** yielded the alcohol **20** upon reduction, but **26** did not.
(15) In addition a minor product (~5%) was identified as the α,β-unsaturated ketoamide **3a** in the succeeding paper.[17] Since **26** and **27** are stable under the reaction conditions, **3a** probably arises directly from **25**.
(16) Sodium borohydride reduction of **27** gave exclusively the undesired alcohol.
(17) Part II following by T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi.
(18) We (M.A., L.V.D., T.F., and Y.K.) thank Harvard University and Hoffmann-La Roche Co. for their financial assistance.

Department of Chemistry **M. Aratani**
Harvard University **L. V. Dunkerton**
Cambridge, Massachusetts 02138 **T. Fukuyama**
Y. Kishi*

Faculty of Pharmacy **H. Kakoi**
Meijo University **S. Sugiura**
Showa, Nagoya, Japan **S. Inoue**

Received March 17, 1975

Synthetic Studies on Histrionicotoxins. II.[1] A Practical Synthetic Route to (±)-Perhydro- and (±)-Octahydrohistrionicotoxin

Summary: The first total synthesis of (±)-octahydrohistrionicotoxin (**9b**), one of the actual naturally occurring histrionicotoxins, and a practical synthesis of (±)-perhydrohistrionicotoxin (**9a**) have been achieved by using cyclization of the α,β-unsaturated ketoamide **3** to the spiro ketolactam **5** as a key reaction.

Sir: In the preceding paper[1] we reported a stereocontrolled synthesis of perhydrohistrionicotoxin (**9a**). However, this route is still unsatisfactory from the practical point of view, because of too many steps required and its low overall yield from the commercially available starting material. In this communication we describe a practical synthetic route to (±)-perhydrohistrionicotoxin (**9a**) and the first total synthesis of (±)-octahydrohistrionicotoxin (**9b**), one of the actual naturally occurring histrionicotoxins.[2,3] The key step of this new route was developed based on our previous observation[1] that the spiro ketolactam **5a** is stable under strong acidic and basic conditions, which would suggest a possibility to cyclize the α,β-unsaturated ketoamide **3a** to the spiro ketolactam **5a**.

2-Butylcyclohexane-1,3-dione[4,5] (**1a**) (mp 112–113°, lit.[4] mp 115–116°) was synthesized from methyl 4-(chloroformyl)butyrate by two operations [(1) $(C_5H_{11})_2Cd$ in benzene, (2) KO-*t*-Bu in ether]. The cyclohexanedione **1a** was converted to the vinylcyclohexenone[5] **2a** (oil) by two operations [(1) EtOH-H^+, (2) CH_2=$CHMgBr$ in THF]. Michael addition of methyl malonamate to **2a** ($NaOCH_3$ in CH_3OH), followed by hydrolysis of the ester group (aqueous NaOH), neutralization (aqueous HCl), and decarboxylation (100° in dioxane), yielded the α,β-unsaturated ketoamide[5] **3a** (viscous oil) in 45% overall yield from methyl 4-(chloroformyl)butyrate.

The expected cyclization of **3a** was most efficiently achieved by treatment with ethyl orthoformate in ethyl alcohol containing camphorsulfonic acid, followed by aqueous acetic acid work-up, and a mixture of the epimeric ketolactams[5,6] **4a** (two parts) and **5a** (one part) was isolated in almost quantitative yield.

Parallel experiments, starting from methyl 4-(chloroformyl)butyrate and dipentenylcadmium, gave the corresponding 2-(Δ^3-butenyl)cyclohexane-1,3-dione[5] (**1b**) (mp 92.5–93.5°, lit.[7] mp 95–97.5°), the vinylcyclohexenone[5] **2b** (oil), the α,β-unsaturated ketoamide[5] **3b** (viscous oil), and then an epimeric mixture of the spiro ketolactam[5,6] **4b** (two parts) and **5b** (one part) in 45% overall yield.

The epimeric mixture of the spiro ketolactams **4a** and **5a** was converted to (±)-perhydrohistrionicotoxin (**9a**) by the established method.[1] Parallel experiments allowed the conversion of the epimeric mixture of the spiro ketolactams **4b** and **5b** to (±)-octahydrohistrionicotoxin (**9b**). Namely, equilibration of the mixture in methylene chloride containing sodium methoxide at room temperature gave a new mixture of **5b** (four parts) and **4b** (one part), which was reduced to the alcohol[5] **6b** (mp 181–183°) by lithium in ammonia at −78° in 50% yield. The undesired alcohols (epimers at the 7 position), easily separated by a short silica gel column chromatography, can be recycled by Jones oxidation, equilibration, and reduction. The structure of the alcohol **6b** was confirmed by spectroscopic data as well as by reducing and identifying the product with the authentic **6a**.[1] The lactam alcohol **6b** was converted into the corresponding thiolactam alcohol[5] **7b** (mp 171–172°) in 90% yield by three operations [(1) Ac_2O–Py, (2) P_2S_5, (3) OH−]. Protection of the alcoholic function of **7b** as the THP derivative, thioimino ether formation with Meerwein reagent, $AlH(i\text{-}Bu)_2$-catalyzed alkylation with pentenyllithium,[1] and deprotection of the alcoholic function yielded the ketimine[5] **8b**, which was immediately reduced with AlH_3 in cyclohexane to yield a mixture of (±)-octahydrohistrionicotoxin (**9b**, six parts) and *epi*-octahydrohistrionicotoxin (one part). The (±)-octahydrohistrionicotoxin (**9b**) can be