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.

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(1) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, *Helv. Chim. Acta*, **57**, 2597 (1974), and references therein.
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(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.

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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.

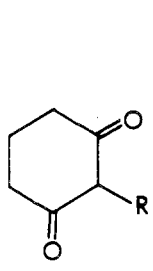
Sir: In the preceding paper[1] we reported a stereocontrolled synthesis of perhydrohistrionicotoxin (**9a**). However, this route is still unsatisfactory from the practical point of view, because of too many steps required and its low overall yield from the commercially available starting material. In 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.

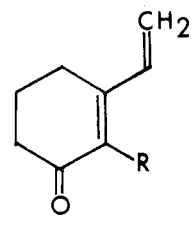
The expected cyclization of **3a** was most efficiently achieved by treatment with ethyl orthoformate in ethyl alcohol containing camphorsulfonic acid, followed by aqueous acetic acid work-up, and a mixture of the epimeric ketolactams[5,6] **4a** (two parts) and **5a** (one part) was isolated in almost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

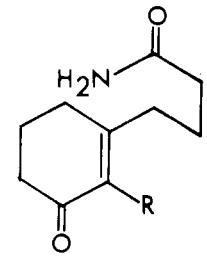
The epimeric mixture of the spiro ketolactams **4a** and **5a** was converted to (±)-perhydrohistrionicotoxin (**9a**) by the established method.[1] Parallel experiments allowed the conversion of the epimeric mixture of the spiro ketolactams **4b** and **5b** to (±)-octahydrohistrionicotoxin (**9b**). 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



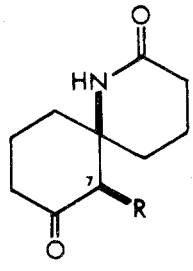
1a, b



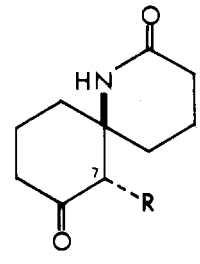
2a, b



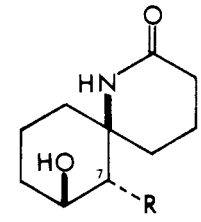
3a, b



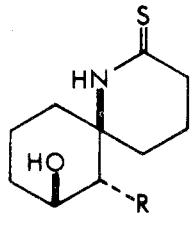
4a, b



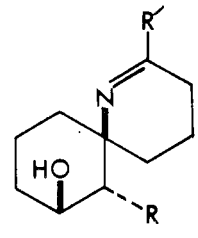
5a, b



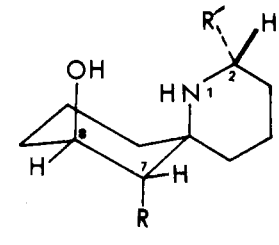
6a, b



7a, b



8a, b



9a, b

a series : $R=CH_2CH_2CH_2CH_3$, $R'=CH_2CH_2CH_2CH_2CH_3$

b series : $R=CH_2CH_2CH=CH_2$, $R'=CH_2CH_2CH_2CH=CH_2$

separated by silica gel TLC or by direct recrystallization as its hydrochloride. The overall yield of **9b** from **7b** was ~70%. The structure of the synthetic octahydrohistrionicotoxin[5] **9b** (melting point in a sealed tube, 151–154° as its hydrochloride) was confirmed by spectroscopic data (MS, NMR, ir) and also by reducing and identifying it with authentic perhydrohistrionicotoxin (**9a**).[1]

Thus, racemic octahydro- and perhydrohistrionicotoxin can be synthesized in ~14% overall yield (the conditions have *not* been optimized; the recycle of the undesired alcohols is *not* counted) from the commercially available methyl 4-(chloroformyl)butyrate by simple operations. It is also possible to apply the procedure for the synthesis of octahydro- and perhydrohistrionicotoxin analogs and of decahydrohistrionicotoxins. The detailed results of the physiological tests of these synthetic materials will be reported elsewhere. Further extension of the present procedure for the synthesis of additional histrionicotoxins is in progress in our laboratories.[8]

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References and Footnotes

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(2) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, *Helv. Chim. Acta*, **57**, 2597 (1974), and references therein.
(3) Although octahydrohistrionicotoxin is one of the *minor* alkaloids of the Columbian "arrow poison frog", *Dendrobates histrionicus*,[2] a population of this frog in northern Ecuador was recently found by Dr. J. W. Daly and Dr. C. W. Myers to contain octahydrohistrionicotoxin as a *major* alkaloid (private communication from Dr. B. Witkop).
(4) K. W. Rosenmund and H. Bach, *Chem. Ber.*, **94**, 2394 (1961).
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(8) We thank Harvard University and Hoffmann-La Roche Co. for generous financial assistance.

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