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A TOTAL SYNTHESIS OF d,l-HISTRIONICOTOXIN[1]

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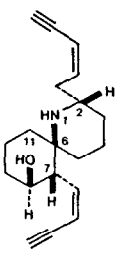
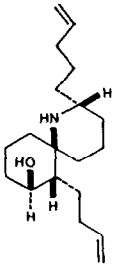
Abstract: The first total synthesis of d,l-histrionicotoxin (1) from the spirolactam (5) is reported.

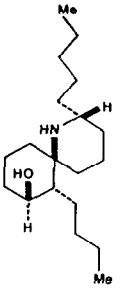
In recent years considerable synthetic interest has been addressed to the histrionicotoxin family[2,3] of alkaloids; in particular, many successful syntheses of perhydrohistrionicotoxin (3), the hydrogenation product of histrionicotoxin, have been recorded.[4] However, naturally occurring histrionicotoxins except octahydrohistrionicotoxin (2)[5] have not yet been synthesized. In this communication we would like to report the synthesis of d,l-histrionicotoxin (1), the parent alkaloid of this family.[6]



1 : histrionicotoxin



2 : octahydrohistrionicotoxin

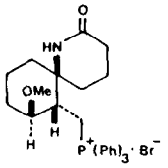


3 : perhydrohistrionicotoxin

Upon examination of negative but valuable experimental results accumulated in our laboratories over the years, it became obvious that certain synthetic schemes were not applicable to the synthesis of historionicotoxin even though they initially seemed attractive. For example, our original intention had been to use Wittig olefination to introduce simultaneously both cis-enyne side-chains. However, we noted that the phosphorane generated from 4 produced no recognizable amount of the desired product on treatment with 3-(t-butyldimethylsilyl)propynal. Thus, it was decided to introduce the side-chain at the C.7 position in a stepwise manner using a cyclic intermediate for selective formation of the cis-olefinic bond.

Our synthesis began with the known spirolactam 5,[5] which was converted into the enol ether 6[7] (mp 175-177°C) in 4 steps, i.e. 1. OsO_4-$NaIO_4$/dioxane-H_2O/RT, 2. 1 N NaOH/MeOH/RT, 3. Ac_2O/py/RT, and 4. 180°C (11 mm Hg). Bromination (Br_2/MeOH-CH_2Cl_2) of 6, followed by dehydrobromination (DBU/DMSO/140°C), gave a diastereomeric mixture of unsaturated methylacetals.[8] Hydrolysis (AcOH-H_2O/60°C) of this mixture, followed by reduction ($NaBH_4$/THF-H_2O) and then acetylation (Ac_2O/py), gave the diacetate 7 (mp 208-209°C). The spin-spin coupling constant (J = 11.3 Hz) of the olefinic protons clearly indicated that the cis-olefin formed in the dehydrobromination step was retained unchanged throughout the transformation. The overall yield of 7 from 5 was 35-40%. Thiolactamization (P_2S_5/py/80°C) of 7 and then condensation with ethyl 2-bromoacetoacetate ($NaHCO_3$/CH_2Cl_2/RT)[9] gave the α-acetyl vinylogous urethane 8 (oil) in 60% overall yield.

One of the major difficulties met in this particular synthetic route was the timing of functionalization of the lower side-chain. For example, all attempts to oxidize the allylic alcohol 9a or 9b were unsuccessful apparently due to a vinylogous Grob-type fragmentation of the intermediate. Thus, we were forced to construct the lower side-chain at an early stage of synthesis to prevent the lone pair electrons of the nitrogen from participating in the undesired fragmentation. It proved possible to saponify selectively the primary acetate of 8 (NaOH/H_2O-MeOH/-20°C) and then to oxidize to the desired unsaturated aldehyde (PCC/CH_2Cl_2/RT), which was immediately subjected to the 3-step sequence of reactions (1. $(Ph)_3P^+CH_2ClCl^-$/



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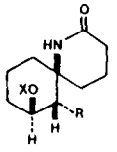
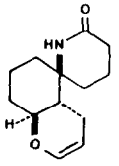
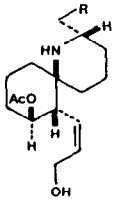


5 : R=$CH_2CH_2CH{=}CH_2$, X=Ac

7 : R=$CH{\overset{c}{=}}CHCH_2OAc$, X=Ac

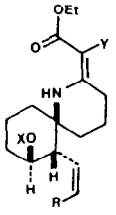


6



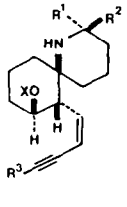
9a : R=$CH{\overset{c}{=}}CHC{\equiv}CH$

9b : R=CO_2Et



8 : R=CH_2OAc, X=Y=Ac

10 : R=$C{\equiv}CSi(Me)_3$, X=Ac, Y=H



11a: R^1=CH_2CO_2Et, R^2=H, R^3=$Si(Me)_3$, X=Ac

11b: R^1=H, R^2=CH_2CO_2Et, R^3=$Si(Me)_3$, X=Ac

12 : R^1=CH_2CH_2OH, R^2=H, R^3=$Si(Me)_3$, X=Ac

13 : R^1=$CH_2CH_2P^+(Ph)_3Br^-$, R^2=R^3=H, X=Ac

n-BuLi/THF/-78°C,[10] 2. NaOEt/EtOH/50°C,[9] 3. CH_3Li/TMSCl/THF[10]) to furnish the protected cis-enyne 10 (oil) in 37% overall yield from 8. The spin-spin coupling constant of the olefinic protons was found to be 10.1 Hz, which confirmed that the stereochemical integrity of the cis-olefinic bond was preserved throughout this sequence.

We next turned our attention to the completion of the upper side-chain. Although reduction of the vinylogous urethane group was unexpectedly difficult with $LiAlH_4$, Super-Hydride or AlH_3,[11] reduction was quite facile with borohydride-based reagents. A 1:1 ratio of the amino esters 11a (38% isolated yield; oil) and 11b (38% isolated yield; mp 94-95°C) was obtained using $NaBH_3CN$ in cyclohexane at room temperature. The stereochemistry of 11a was tentatively assigned, based on the observation that 11b was the sole product obtained by reduction of 10 with $NaBH_4$ in ethanol.[11] This assignment was later confirmed by the successful synthesis of histrionicotoxin from 11a. The amino ester 11a was reduced ($LiAlH_4$/THF) and acetylated (Ac_2O/py) to yield the corresponding diacetate. It again proved possible to saponify selectively the diacetate (NaOH/MeOH/0°C) to the monoacetate 12 (mp 132-133°C). Although the yield of this reaction was only moderate (31% direct yield; 78% yield based on the recovered diol and the starting material), the ease with which the diol product and the starting material were recycled made the procedure quite practical; the overall yield of 12 from 11a was 63% after two recycles of the diol. Desilylation (n-Bu_4NF/THF) and then mesylation ($MsCl/Et_3N/CH_2Cl_2$) of 12 were followed by formation of the corresponding hydrochloride ($HCl/Et_2O/CH_2Cl_2$), which acted to prevent undesired cyclization of the amino mesylate in the subsequent transformation.[12] Treatment of the hydrochloride with anhydrous lithium bromide (DMF/50°C) and then with excess triphenylphosphine (CH_3CN/160°C) gave the phosphonium salt 13 in 35% overall yield. Wittig reaction of the phosphorane generated from 13 (LDA/THF/RT) with 3-(t-butyldimethylsilyl)-propynal, followed by desilylation (n-Bu_4NF/THF) and then deacetylation (NaOH/MeOH), produced a 24:1 ratio (NMR) of cis- and trans-enynes,[13] which were separated by preparative tlc to yield d,l-histrionicotoxin (1) (18% overall yield[14]) and its trans isomer (0.8% overall yield). On comparison of spectroscopic (^{1}H-NMR, MS, UV) and tlc data, the synthetic substance was identical with natural histrionicotoxin.[15]

Acknowledgment: Financial support from the National Institutes of Health (Grant NS 12108) is gratefully acknowledged.

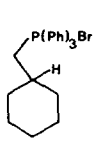
References and Footnotes

1. Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.
2. a. J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, Proc. Natl. Acad. Sci. USA, 68, 1870 (1971). b. T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, and B. Witkop, Helv. Chim. Acta, 57, 2597 (1974).
3. For reviews on histrionicotoxin alkaloids, see a. J. W. Daly, "Alkaloids of Neotropical Poison Frogs (Dendrobatidae)", in Progress in the Chemistry of Organic Natural Products, Vol. 41, ed. W. Herz, H. Grisebach and G. W. Kirby, Springer-Verlag, New York, 1982, p 247. b. B. Witkop and E. Gossinger, "Amphibian Alkaloids" in The Alkaloids, Vol. 21, ed. A. Brossi, Academic Press, New York, 1983, p 168.
4. The total syntheses of perhydrohistrionicotoxin reported before the fall of 1981 are well covered in reviews: a. see reference 2a. b. Y. Inubushi and T. Ibuka, Heterocycles, 17, 507 (1982). For the syntheses reported since then, see A. B. Holmes, K. Russell, E. S. Stern, M. E. Stubbs, and N. K. Wellard, Tetrahedron Lett., 25, 4163 (1984) and references cited therein.

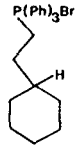
5. T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, J. Org. Chem., 40, 2011 (1975).
6. Taken in part from the dissertations of Matsuhiko Aratani (Nagoya University, 1976) and Stephen Colwell Carey (Harvard University, 1983).
7. All the new substances described in this paper were satisfactorily characterized [MS, NMR, IR, UV, and elemental analysis (for crystalline substances)].
8. As anticipated, dehydrobromination took place exclusively in the desired direction.
9. The method reported by M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser [Helv. Chim. Acta, 54, 710 (1971)] was applied to 2-bromoacetoacetate since the α-acyl group of the product could be removed under mild basic conditions: see, H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, J. Am. Chem. Soc., 99, 2818 (1977).
10. E. J. Corey and R. A. Ruden, Tetrahedron Lett., 1495 (1973).
11. The stereochemistry outcome of hydride reduction was investigated on similar systems: M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, J. Org. Chem., 40, 2009 (1975). AlH_3 reduction yielded the natural stereoisomer at the C.2 position as the major product while $NaBH_4$ and $LiAlH_4$ reduction yielded the unnatural stereoisomer.
12. The free base of the mesylate was labile — it cyclized gradually to an azetidine at room temperature — whereas the free base of the corresponding bromide was stable as one might anticipate based on the soft-hard acid-base principle.
13. Since there was only one example known [P. C. Wailes, Aust. J. Chem., 13, 173 (1959)] for this type of Wittig reaction, we studied the stereoselectivity of the coupling reactions of 4 model compounds i-iv with TMS-C≡C-CHO (Table summarizes ratios of cis- and trans-enynes formed from i-iv under the specified conditions. Combined, isolated yields of cis- and trans-enynes are given in parantheses. Dashed lines indicate no coupling reactions conducted under the specified conditions). It is interesting to note the remarkable inverse temperature-dependency observed for ii and iii. The Wittig process utilizing the alternative combination of the reactants is known preferentially to produce trans-enynes (for examples, see reference 10).

Table

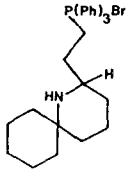
conditions	i	ii	iii	iv
n-BuLi/THF/RT	10:1 (81%)	14:1 (79%)	10:1 (45%)	12:1 (92%)
n-BuLi/THF/-78°C	21:1 (85%)	5:1 (70%)	2.5:1 (35%)	---
n-BuLi/TMEDA-THF (1:4)/RT	---	7:1 (88%)	7:1 (60%)	---
n-BuLi/TMEDA-THF (1:4)/-78°C	30:1 (95%)	5:1 (79%)	---	---
$KN(TMS)_2$/TMEDA-THF (1:4)/RT	---	7:1 (87%)	7:1 (57%)	---
$KN(TMS)_2$/TMEDA-THF (1:4)/-78°C	39:1 (76%)	3:1 (78%)	---	---



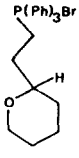
i



ii



iii



iv

14. This experiment was carried out on an 11-mg scale. The scale of the experiment seemed to be the primary reason for the low chemical yield — compare with the yield of iii in reference 13.
15. We are indebted to Dr. J. Daly for a sample of natural histrionicotoxin.

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