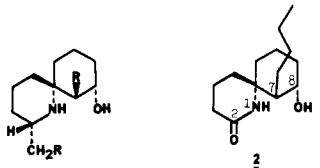
A Novel Synthesis of (±)-Perhydrohistrionicotoxin

Summary: A formal total synthesis of (±)-perhydrohistrionicotoxin is reported, which utilizes an intramolecular ene reaction for construction of the spirocyclic skeleton.

Sir: The histrionicotoxins (**1a–c**), originally brought to attention by the investigations of Witkop,[1] have since attracted considerable interest amongst synthetic chemists[2] due to both their unusual structures and their very potent neurotoxic activity, which has been shown to result from blocking of postsynaptic membrane depolarization.[3]

Previous total syntheses of (±)-PHTX (**1c**) have established that hydroxy lactam **2** is an efficient precursor to **1c**,[2a-c] and several syntheses of **2** have now been developed.[2a-c] Presently, we report a conceptually direct approach to the synthesis of **1a** via **2**, which differs significantly from previous approaches in that the C_7 substituent is introduced *after* formation of the spirocyclic nucleus of **2**, and which illustrates the application of several new synthetic methods for the preparation of such compounds.



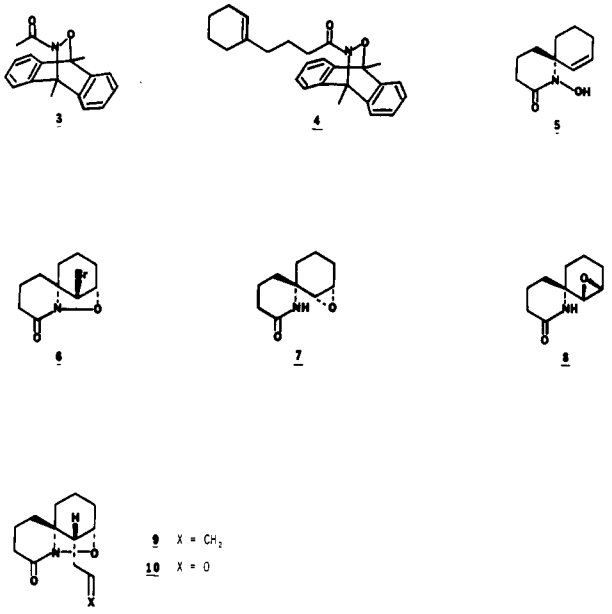
1a R = -CH=CH-C≡C-H

1b R = $-(CH_2)_2-CH=CH_2$

1c R = C_4H_9

Alkylation of the known,[4] readily available, Diels–Alder adduct **3** of (nitrosocarbonyl)methane with 9,10-dimethylanthracene (LDA, THF–HMPA, −78 °C, ca. 1 h, then −20 °C, 12 h) with (2-iodoethyl)-1-cyclohexene[5] proceeds smoothly to give **4** in 72% isolated yield after purification by column chromatography over silica gel.[6] Thermolysis of **4** in toluene at reflux for 40 min, followed by rapid chromatography over silica gel, then afforded the key spirocyclic hydroxamic acid **5** (mp 123–125 °C) in quantitative yield, via intramolecular ene reaction[7] of an intermediate acylnitroso compound.

Stereocontrolled introduction of the C_8-hydroxyl substituent was readily achieved, since the unsaturated hydroxamic acid **5** already possesses a highly nucleophilic (and extraneous) hydroxyl function situated on the correct face (α as shown below) of the carbocyclic six ring. Thus, treatment of a methylene chloride solution of **5** with 1



equiv of *N*-bromosuccinimide at 0 °C afforded, essentially instantaneously, the bromide **6**, mp 180 °C dec, in 83% yield after rapid chromatography on alumina.[8]

Introduction of an appropriate four-carbon substituent at C_7, the only significant remaining task, was expected to be a formidable problem since Kishi had previously reported that *both* epoxides **7** and **8** were opened by lithium di-*n*-butylcuprate at C_8, rather than the more conjested C_7 position.[2] Additionally, **6** was found to be quite labile with respect to reductive elimination to reform hydroxamic acid **5**. A solution to these problems was found in a one-electron free-radical chain process.[9,10] Treatment of **6** with allyltri-*n*-butyltin[11] (2.0 equiv) and 0.15 equiv of azobis(isobutyronitrile) in refluxing benzene for 5 h with rigorous exclusion of oxygen cleanly afforded the C_7-allyl derivative **9**, mp 72 °C, as a *single stereoisomer* in 88% yield.[12] A tentative assignment of stereochemistry proved possible by comparison of the ^1H NMR spectra of **9** and **6**, which strongly suggested[13] that incorporation of the allyl unit had proceeded exclusively from an equatorial direc-

(1) (a) Witkop, B. *Experientia* **1971**, *27*, 1121. (b) Daly, J. W.; Karle, I.; Meyers, W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870. (c) Tokuyama, T.; Venoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597. (d) Karle, I. *J. Am. Chem. Soc.* **1973**, *95*, 4036.

(2) (a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (b) Aratani, M.; Dunkerton, C. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009. (c) Fukuyama, T.; Dunkerton, C. V.; Aratani, M.; Kishi, Y. *Ibid.* **1975**, *40*, 2011. (d) Corey, E. J.; Petrzilka, M.; Veda, Y. *Helv. Chim. Acta* **1977**, *60*, 2294. (e) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411.

(3) Elliott, J.; Raffery, M. A. *Biochem. Biophys. Res. Commun.* **1977**, *77*, 1347.

(4) Kirby, G. W.; Sweeny, J. C. *J. Chem. Soc., Chem. Commun.* **1973**, 704.

(5) (a) This material was prepared by treatment of (2-hydroxyethyl)-1-cyclohexene[5b] with *N*-bromosuccinimide and triphenylphosphine in methylene chloride, followed by reaction of the derived bromide with sodium iodide in acetone at 23 °C. (b) Benkeser, R. A.; Arnold, C., Jr.; Lambert, R. F.; Thomas, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 6042.

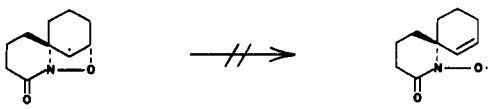
(6) All stable, isolated intermediates described herein gave appropriate NMR, IR, and mass spectra and correct elemental analyses and/or high-resolution mass spectral data.

(7) (a) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, 1185. (b) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007.

(8) NMR examination of the crude reaction product after evaporation of methylene chloride reveals that **6** is formed quantitatively; some material is lost upon chromatography over alumina. Complete removal of succinimide could not be effected either by recrystallization of **6** or by chromatography on silica gel.

(9) For previous simple examples of such a process (which were reported to afford low yields) note: (a) Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973**, *56*, C11. (b) Grignan, J.; Pereyre, M. *Ibid.* **1973**, *61*, C33.

(10) It is of interest that the intermediate radical derived from **6** should be stable toward ring opening to generate the corresponding acylnitroxyl radical, since such radicals are known to be especially stable. This result was anticipated on the basis that during cleavage of the C–O bond to afford the acylnitroxyl radical, odd-electron density would de-



velop on oxygen in an orbital *orthogonal* to the amide π system, thus imposing a significant kinetic barrier for such a cleavage.

(11) This material was prepared according to the procedure of Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797.

(12) (a) Compound **9** is easily isolated (in sufficiently pure form for most purposes) by partitioning the crude reaction product between acetonitrile and pentane (to remove excess allyltri-*n*-butyltin and tri-*n*-butyltin bromide) followed by evaporation of acetonitrile. (b) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

(13) This assignment was based on the observation that **6** shows a triplet, J = 3 Hz for the equatorial proton at C_8, which appears as a doublet, J = 3 Hz, in **9**.

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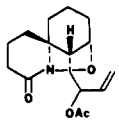
tion, whereas axial incorporation was, in fact, desired for the preparation of **2**. This assignment was further corroborated by subsequent transformations as detailed below.

Oxidative cleavage of the unsaturation in **9** (OsO_4, $NaIO_4$, aqueous THF, 0 °C) gave aldehyde **10** in 89% yield. Attempted incorporation of a two-carbon fragment by Wittig reaction with ethylidenetriphenylphosphorane proved unexpectedly difficult and isolated yields of the desired product in excess of ca. 40% could not be realized despite extensive experimentation. Isolation of product was also complicated by its low solubility in most organic solvents and the unusually high polarity found to be characteristic of this ring system. However, aldehyde **10** could be easily converted to the desired butyl compound (**13**) in 71% overall yield by the following series of reactions, which were conveniently conducted without purification of intermediates: (1) reaction with 1.1 equiv of vinylmagnesium bromide in THF at −78 °C for 15 min, followed by addition of excess (3 equiv) acetic anhydride and warming to room temperature, to afford **11**; (2) palladium-catalyzed elimination of acetic acid[14] (0.01 equiv of $Pd(OAc)_2$, 0.10 equiv $P(Ph)_3$, dioxane reflux) to yield diene **12**; and (3) hydrogenation over Adams catalyst in ethyl acetate.



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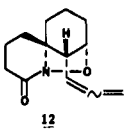
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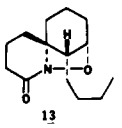
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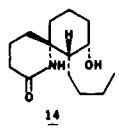

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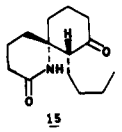

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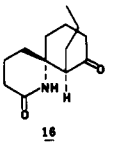

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Reduction[15] of **13** with 6% sodium amalgam in isopropyl alcohol at room temperature cleanly afforded the hydroxy lactam **14** in 94% isolated yield. Comparison with authentic **2** clearly revealed that **14** was in fact epimeric with **2** [silica gel, TLC R_f values of 0.29 and 0.35 for **2** and **14**, respectively, in MeOH–$CHCl_3$ (8:92)] and necessitated an adjustment of stereochemistry at C_7 along previously reported lines. Oxidation of **14** with Me_2SO–oxalyl chloride according to the procedure of Swern[16] afforded ketone **15** essentially quantitatively, which was epimerized to a 1:4 mixture of **15** and **16** according to the published procedure.[2b] Reduction as described by Kishi and co-workers[2b] then yielded **2**, which was identical with an authentic sample by the usual criteria (^1H NMR, IR, ^{13}C NMR, MS, TLC, HPLC).[17]

Although the approach delineated above suffers from a loss of stereocontrol in the incorporation of the allyl unit, it is nonetheless intriguing that incorporation of the allyl unit is, in fact, stereoselective. Further investigations and applications of the ene and organotin methodologies outlined herein are being pursued.[18]

Registry No. 1c, 55254-30-3; **2**, 55228-76-7; **3**, 51029-28-8; **4**, 82537-60-8; **5**, 82570-97-6; **6**, 82537-61-9; **9**, 82537-62-0; **10**, 82537-63-1; **11**, 82537-64-2; **12**, 82537-65-3; **13**, 82537-66-4; **14**, 82570-98-7; **15**, 56459-12-2; **16**, 56459-13-3; (2-iodoethyl)-1-cyclohexene, 82201-80-7; allyltri-*n*-butyltin, 24850-33-7.

Supplementary Material Available: Full experimental details including spectra and analytical data (10 pages). Ordering information is given on any current masthead page.

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Alkynylquinones. Synthesis of 2-Alkynyl-5-methoxy-1,4-benzoquinones

Summary: An experimentally simple and efficient synthesis of 2-alkynyl-5-methoxy-1,4-benzoquinones is described. This involves the 1,2-addition of lithium acetylides to 4,5-dimethoxy-1,2-benzoquinone to give the quinols **2a–i**. Hydrolysis of these adducts with dilute acids gives the quinones in overall yields ranging from 61% to 92%.

Sir: Recently we described an efficient method for the synthesis of 2,5-dialkylated 1,4-benzoquinones involving the 1,2-addition of organolithium reagents to 2,5-dialkoxy-1,4-benzoquinones followed by acid hydrolysis of the resulting adducts.[1] Here we report an extension of this methodology that provides an experimentally simple and high-yield procedure for the construction of 2-alkynyl-5-methoxy-1,4-benzoquinones. Such compounds are of potential interest since alkynylquinones have received very little attention.[2] In addition, the fact that alkynyl groups can be converted to a large variety of other functionalities,[3] along with the observation that many natural quinones possess the 2-alkylated 5-oxygenated 1,4-benzoquinone framework,[4] provided a further stimulus for this study. Of particular interest will be the utilization of alkynylcyclohexadienones, **2**, and alkynylquinones, **3**, for the synthesis of prodrugs. Indeed, 2-alkynyl-5-methoxy-1,4-benzoquinones are ideally suited to function as precursors to bioreductive alkylating agents.[5]

Specifically, 4,5-dimethoxy-1,2-benzoquinone (**1**)[6] was treated with a variety of lithium acetylides to give excellent yields (70–95%) of the corresponding 6-alkynyl-6-hydroxy-3,4-dimethoxy-2,4-cyclohexadienones **2a–i**. Treatment of adducts **2a–g** with dilute sulfuric acid resulted in hydrolysis of the acid-sensitive β-hydroxy enol

(14) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075.
(15) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(16) (a) Okamura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(17) We thank Professor Yoshito Kishi for a generous sample of hydroxy lactam **2**. We also thank Dr. Larry Blaszczak of Eli Lilly Co. for discussing his own independent investigations of similar organotin chemistry prior to publication.

(1) Moore, H. W.; Sing, Y. L.; Sidhu, R. S. *J. Org. Chem.* **1980**, *45*, 5057.
(2) To our knowledge, the only other examples of conjugated alkynylquinones are these described in ref 1.
(3) Viehe, H. G. "Chemistry of Acetylenes"; Marcel Dekker: New York, 1969. Patai, S., Ed, "The Chemistry of the Carbon–Carbon Triple Bond"; Wiley: New York, 1978.
(4) Thompson, R. H. "Naturally Occurring Quinones"; Academic Press: New York, 1971.
(5) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.
(6) This quinone can be easily prepared in 15-g lots by the iodate oxidation of catechol in methanol. See Itoh, Y.; Kakuta, T.; Hirano, M.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2169.

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