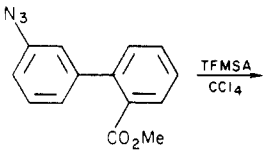

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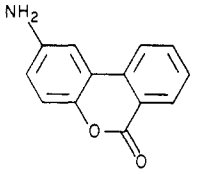

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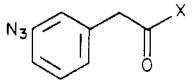
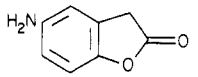


19, X = OH
20, X = NH_2



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and heterocyclic rings are currently under investigation and will be reported soon.

Acknowledgment. We thank the National Science Foundation for a grant (No. CHE-78-04805) in support of this work.

Registry No. 3, 83542-55-6; 4, 5369-22-2; 5, 76302-58-4; 6, 83527-88-2; 7, 83527-87-1; 8, 83527-89-3; 9, 83527-90-6; 10, 83527-91-7; 11, 83527-92-8; 12, 22161-41-7; 13, 83527-93-9; 14, 83527-95-1; 15, 83527-94-0; 16, 21408-]6-2; 17, 83527-98-4; 18 (isomer 1), 83527-99-5; 18 (isomer 2), 83527-00-1; 19, 83527-01-2; 20, 83527-02-3; 21, 83527-03-4; methyl 3-nitrobiphenyl-2′-carboxylate, 83527-96-2; methyl 3-aminobiphenyl-2′-carboxylate hydrochloride, 83527-97-3.

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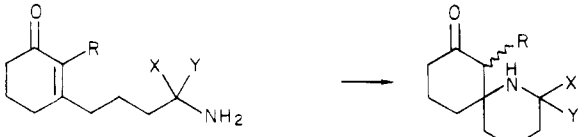
Received August 6, 1982

Trimethylsilyl Iodide Catalyzed Spirocyclization of Amines. Synthesis of Perhydrohistrionicotoxin

Summary: A trimethylsilyl iodide catalyzed Michael reaction of an enone amine and a trimethylsilyl iodide catalyzed S_N2' spirocyclization of an allylic alcohol amine are the crucial reactions in two new syntheses of perhydrohistrionicotoxin.

Sir: The histrionicotoxins, a class of spirocyclic alkaloids isolated from the skin of the frog, *Dendrobates histrionicus*,[1] have received considerable attention from synthetic chemists because of their distinctive structural features and their unique properties as inhibitors of the ion transport mechanism of the cholinergic receptor.[2] An intensification of interest in these alkaloids has recently occurred based on reports that a variety of structurally simplified analogues maintain high levels of neurological activity.[3,4] Perhydrohistrionicotoxin (1; PHTx), a non naturally occurring congener of histrionicotoxin that possesses comparable bioactivity, has served as the focus of this interest with several total syntheses[5-8] and synthetic approaches[9-11] having been reported, including our own[12] synthesis of 1, in which the key spirocyclization is achieved with use of organopalladium chemistry.

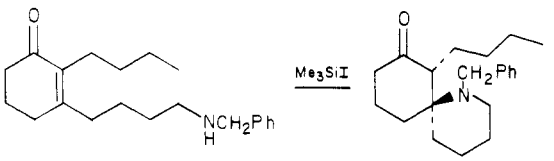
A number of investigators have explored entry into the [5,5]-1-azaspirocyclic ring structure of 1 via a Michael reaction with only mixed success. Corey[5a] has studied reactions of the tetrasubstituted enone **2a** but could not effect its cyclization. Michael reactions of the trisubstituted enone **2b** did proceed, but only to give a 1:1 mixture of isomers at the carbon bearing the *n*-pentyl group.[5a] Magnus[11] has reported the acid-catalyzed Michael reaction of the enone amine **2c**, but no results on the more pertinent tetrasubstituted enone were included in this work. The enone lactam **2d** has been successfully cyclized by Kishi[6] achieving a 1:2 ratio of desired to undesired ketones (**3a**/**3b**), which could be epimerized to only a 4:1 ratio (**3a**/**3b**).



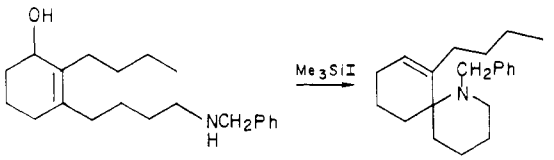
2a, R = *n*-Bu; X = *n*-pentyl; Y = H
2b, R = H; X = *n*-pentyl; Y = H
2c, R = X = Y = H
2d, R = *n*-Bu; X, Y = O

3

We herein report the development of two trimethylsilyl iodide (Me_3SiI)[13] catalyzed amine spirocyclization reactions. The first readily effects the Michael reaction of the tetrasubstituted enone amine **4** under mild conditions, providing **5** with the desired disposition of the *n*-butyl group predominating (5:1). In addition, this ratio can be enhanced to 13:1 by epimerization. The second Me_3SiI reaction catalyzes an intramolecular S_N2' reaction of the allylic alcohol amine **6**, producing the spiro olefin **7**. Conversions of both **5** and **6** to desamyl-PHTx (**8**) have been achieved.



4 5a



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(10) Tuffariello, J. J.; Trybulski, E. J. *J. Org. Chem. Soc.* **1974**, *39*, 3378.
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(12) Godleski, S. A.; Heacock D. J.; Meinhart, J. D.; Van Wallendael, S. *J. Org. Chem.*, submitted for publication.
(13) Trimethylsilyl iodide has found a variety of uses; see Schmidt, A. H. *Adrichim. Acta* **1981**, *14*, 31.

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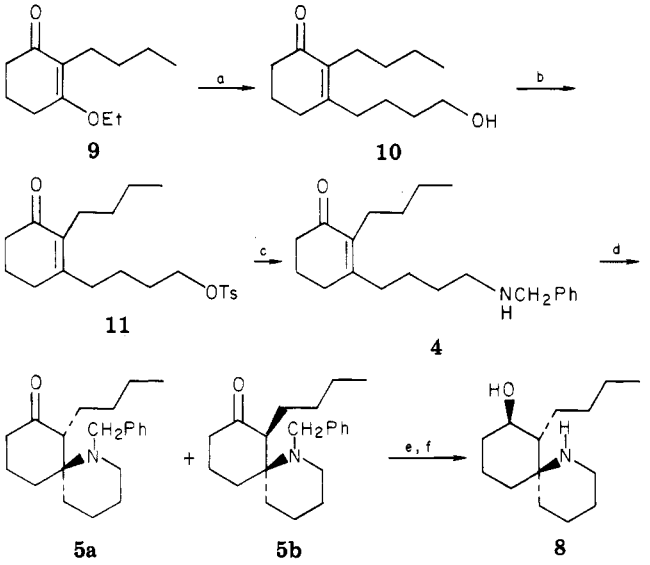
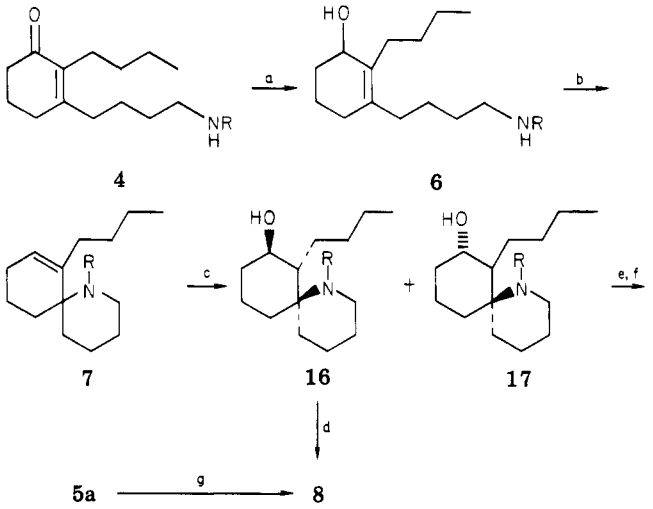
Scheme I[a]



[a] a, $ClMgCH_2CH_2CH_2CH_2OMgCl$, THF, 65%; b, TsCl, py, −10 °C, 8 h, 95%; c, $PhCH_2NH_2$, cat. NaI, Me_2SO, room temp, 18 h, 72%; d, 2.0 equiv of CH_3SiI, 1 equiv of NEt_3, 1 equiv of NaI, CH_3CN, −20 °C, 12 h, 80%; e, NaOMe, CH_2Cl_2, room temp, 24 h; f, Li/NH_3, 2 equiv of MeOH, 65%.

Scheme II[a,b]

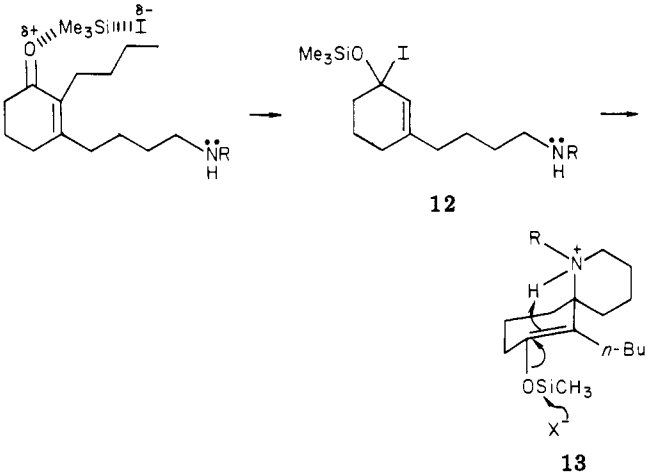


[a] R = CH_2Ph. [b] a, Dibal-H, $PhCH_3$, −50 °C, 5 h, 75%; b, 1.5 equiv of CH_3SiI, 1 equiv of NEt_3, CH_3CN, −20 °C, 40%; c, 1.1 equiv of $BH_3 \cdot Me_2S$; NaOH, H_2O_2, diglyme, 80 °C, 40%; d, 60 psi; H_2, Pd/C, ETOH, 85%; e, Swern oxidation $(COCl)_2$, Me_2SO, NEt_3, −50 °C, 90%; f, NaOMe, CH_2Cl_2, room temp, 24 h; g, Li/NH_3, 2 equiv of MeOH, 65%

We chose as the target of our synthetic efforts desamyl-PHTx (8) on the basis of two considerations: (1) Corey[5b] had previously efficiently converted 8 to PHTx (1): (2) 8 has been found to possess comparable biological activity to PHTx (1).[3]

The preparation of 8 utilizing the CH_3SiI-catalyzed Michael addition reaction is outlined in Scheme I. The sequence is initiated by reaction of the Normant Grignard reagent[14] derived from 4-chlorobutanol with the known vinylogous ester 9,[15] which on acidic workup yields the enone alcohol 10 in 65% yield. Tosylation of the alcohol 10 (TsCl, py, −10 °C, 8 h) provided 11 in 95% yield. Amination of the tosylate with $PhCH_2NH_2$[16] (catalyst NaI, Me_2SO, room temperature, 18 h) gave the precursor for the CH_3SiI reaction (4) in 72% yield. Treatment of 4 with 2 equiv of CH_3SiI in CH_3CN contaiing 1 equiv of NEt_3 and 1 equiv of NaI at −20 °C for 12 h gave the cyclized ketones (**5a**/**5b**) in a 5:1 ratio in 80% yield on the basis of recovered starting material (40% conversion). Epimerization of the ketones (CH_2Cl_2, NaOMe, room temperature 24 h) gave **5a**/**5b** in a 13:1 ratio. Reduction of **5a** using Li/NH_3 and 2 equiv of MeOH[17] neatly effects both debenzylation and completely stereoselective reduction of the ketone, providing desamyl-PHTx in 65% isolated yield. The desamyl-PHTx produced in this way was found to be identical with an authentic sample provided by A. Brossi.

The CH_3SiI reaction is suggested to proceed by the following mechanism. Complexation of the enone by the CH_3Si group occurs and this serves to activate it to nucleophilic addition. Iodide then adds, forming an intermediate allyl iodide (12).[18] That initial iodide trapping of the activated enone occurs rather than immediate amine cyclization is indicated by the following observations: (1) the reaction either does not proceed or proceeds in substantially poorer yield with CH_3SiOAc, CH_3SiOTf, $CH_3SiCOCF_3$; (2) the use of added NaI improves the yield in the reaction. The ability of iodide to act as both a good nucleophile and a good leaving group appears crucial in this process. S_N2' cyclization of the amine on the allyl iodide yields the enol silyl ether 13. The added stereocontrol of the *n*-butyl moiety afforded in this reaction relative to the Kishi lactam Michael reaction is likely due to the enhanced ability of the amine to internally deliver a proton to the enol silyl ether.



Significantly, treament of the enone amine 4 with aqueous HCl or HI in varying concentrations (catalytic to >1 equiv) did *not* result in the observation of cyclized product, even under forcing conditions (80 °C). In fact, reaction of the cyclized ketone **5a** with dilute aqueous HCl at room temperature was found to promote the retro-Michael process. Likewise, treatment of 4 with base (e.g.,

(14) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, *33*, 3013.

(15) Rosenmund, K.; Bach, H.; *Chem. Ber.* **1961**, *94*, 2394, and ref 6.

(16) Benzylamine was used in this sequence because of its relevancy to our previous efforts in this area (ref 12) and because amination with ammonia proved more difficult and offered no advantage in subsequent steps.

(17) Anhydrous Li/NH_3 reduction gave only 16. Use of >2 equiv of a proton source caused significant amounts of Birch reduction of the benzyl group competitive with debenzylation.

(18) Iodide may add "1,4" to the activated enone. We make no attempt to distinguish between these intermediates. There is a report of CH_3SiI addition to enones providing β-iodo silylenol ethers. Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1979**, 2305.

K_2CO_3 or *n*-BuLi) did not result in production of **5a**.[19]

The mild conditions of the CH_3SiI reaction in conjunction with the potential ability to directly isolate an enol silyl ether cyclization product incapable of retro-Michael processes under the reaction conditions make this reaction of considerable possible utility.

The second CH_3SiI reaction serves as an adjunct to our palladium-based methodology[20] in promoting an S_N2' reaction of aminoallylic alcohols. The precursor for this reaction (**6**) was prepared by DiBAL-H reduction ($PhCH_3$, -5 °C, 75%) on the enone amine **4** (Scheme II). Treatment of **6** with 1.5 equiv of CH_3SiI (1 equiv of NEt_3, CH_3CN, -20 °C) effected cyclization of **7** in 40% isolated yield. Comparable yields were obtained with the primary amine **14** (R = H) and the allyl amine **15** (R = allyl) (Scheme II).

Conversion of the spirocyclic olefin (**7**) to desamyl-PHTx (**8**)[12] was accomplished by hydroboration-oxidation (BH_3-Me_2S, 1.1 equiv, THF, room temperature, 19 h, excess H_2O_2, NaOH, diglyme, 80 °C, 10 h,[21] which provided a 2:1 mixture of the isomeric alcohols (**16**/**17**) in 40% yield. Debenzylation of **16** (60 psi, H_2, EtOH, 48 h) yielded **8** in 85% yield. Alternatively the crude oxidation mixture could be converted to a 2:1 mixture of **5a**/**5b** in 33% yield by Swern oxidation.[22] Epimerization and Li/NH_3 reduction again provided **8**.

We have found this reaction to be a useful complement to the palladium methodology in allowing cyclization of, for example, **15**, which could not be effected by Pd(0).[23]

Acknowledgment. Financial support provided for this research by the NIH Grant No. GM-27328 and the CIBA-GEIGY Corp. is gratefully acknowledged. We also thank Professor R. H. Schlessinger for helpful discussions, and A. Brossi and E. Albuquerque for providing a sample of **8**.

Supplementary Material Available: Full experimental data are included (7 pages). Ordering information is given on any current masthead page.

(19) The trimethylsilyl amine derivative of **4** was prepared and found *not* to cyclize on treatment with CH_3SiI, NEt_3 in CH_3CN at -20 °C for 12 h.

(20) 1-Azaspirocycles, Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, 2247.

(21) These conditions for oxidation were provided to us by Professor A. J. Pearson.

(22) The direct oxidation of the hydroboration product to the ketones using dichromate was not successful. The Swern oxidation on the alcohol was run as described in Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *42*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, 1651.

(23) The palladium reaction fails in the case of the *N*-allyl derivative because the catalyst is effectively sequestered by the allylamine and rendered inert.

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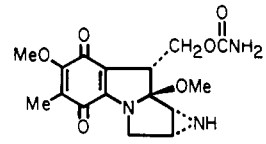
Expeditious Synthesis of 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indoles, Pyrroloindole Quinones, and Related Heterocycles via Nenitzescu-Type Condensation of Quinone Monoketals with Exocyclic Enamino Esters

Summary: Condensation of exocyclic enamino esters with 3-methoxyquinone 4-monoketals gives rise to bicyclic Michael adducts (see Table I) which undergo acid-catalyzed aromatization to 5-methoxypyrroloindole-9-carboxylates suitable for elaboration to mitosenes.

Sir: The antitumor activity of the mitomycin antibiotics (e.g., mitomycin A, **1**)[1] has stimulated a considerable effort



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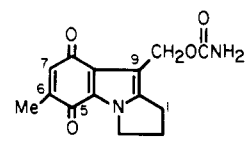

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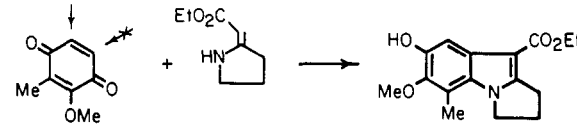
aimed at the synthesis of the natural products, as well as various analogues based on the parent 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole nucleus[1-3] (e.g., mitosene, **2**). Although only one approach has as yet culminated in a total synthesis of the natural mitomycins,[4] the antitumor activity of the simpler mitosenes[1a,5] and the antibacterial properties of related indoloquinones[6] provide incentive for the development of new synthetic routes to these heterocyclic compounds. We have discovered a novel variation of the Nenitzescu indole synthesis[7] which affords directly 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates with a substitution pattern suitable for ready elaboration of the pyrroloindole quinone characteristic of the mitomycins.

Indoles bearing carboxyl and hydroxyl groups at C-3 and C-5 (C-9 and C-7 on mitosene), respectively, are readily prepared by the Nenitzescu reaction of enamino esters and quinones.[7,8] Unfortunately the attractively convergent annelation of toluquinone with ethyl (pyrrolidin-2-ylidene)acetate (**4**) and the corresponding nitrile gives rise to



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mixtures in which the required 7-hydroxy-6-methyl pyrroloindole isomers are minor components.[9] Similarly, and not unexpectedly,[8] we have found that the initial Michael addition step of the Nenitzescu reaction between 2-methoxy-3-methylquinone (**3**)[10] and **4**[11] occurs exclusively "para" to the methoxy group and that the usual equilibrating conditions (1:1 CH_3OH-AcOH, reflux) give the

(1) (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, pp 221-276. (b) Franck, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1-45.

(2) For reviews see: (a) Takahashi, K.; Kametani, T. *Heterocycles* **1979**, *13*, 411-467. (b) Kametani, T.; Takahashi, K. *Ibid.* **1978**, *9*, 293-351.

(3) For recent syntheses of pyrroloindoles and references to others see: (a) Hutchins, C. H.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 4742-4744. (b) Rebek, J., Jr.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173-1177.

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(5) Hodges, J. C.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 1184-1191.

(6) Allen, G. R., Jr.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 1-6 and following papers. For a summary of the biological activity data see ref 1a.

(7) Allen, G. R. *Org. React.* **1973**, *20*, 337-454.

(8) (a) Allen, G. R., Jr.; Pidacks, C.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 2536-2544. (b) Allen, G. R., Jr.; Weiss, M. J. *J. Org. Chem.* **1968**, *33*, 198-200. (c) Littell, R.; Allen, G. R., Jr. *Ibid.* **1968**, *33*, 2064-2069.

(9) (a) Yamada, Y.; Matsui, M. *Agric. Biol. Chem.* **1970**, *34*, 724-728. (b) Yamada, Y.; Matsui, M. *Ibid.* **1971**, *35*, 282-284.

(10) Mandell, L.; Roberts, E. C. *J. Heterocycl. Chem.* **1965**, *2*, 479-480.

(11) Yamazaki, T.; Matoba, K.; Yajima, M.; Nagata, M.; Castle, R. N. *J. Heterocycl. Chem.* **1975**, *12*, 973-979.

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