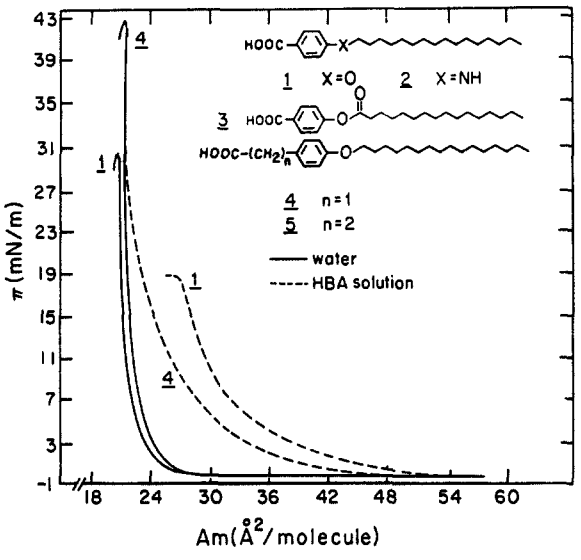


**Figure 2.** Surface pressure–area isotherms of compounds spread on water (full line) and on the supersaturated HBA solution, $8 \times 10^{-2}$ M (broken line). Note that the isotherms for compounds **2** and **3** are similar to that for **1** and the isotherms for **5** and **6** are similar to that for **4**.

specific to the nature of the solute molecules, as was demonstrated by a further experiment in which the subphase was changed from HBA to 4-hydroxyphenylacetic acid. SHG measurements showed that the orientation of **1** was identical ($\theta \sim 24°$) with that found on water, indicating the absence of strong interactions between the molecules of the monolayer and the 4-hydroxyphenylacetic acid subphase.

**Acknowledgment.** We thank E. Gati-Shavit for the synthesis of compound **3** and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial assistance. G.B. acknowledges the support of the Bat-Sheva de Rothschild Fellowship.

(10) Since **1** and **2** have very different nonlinear susceptibilities, the lack of SHG over HBA solutions cannot be attributed to dimers formed between a monolayer molecule and a HBA molecule.

## Total Syntheses of (−)-Histrionicotoxin and (−)-Histrionicotoxin 235A

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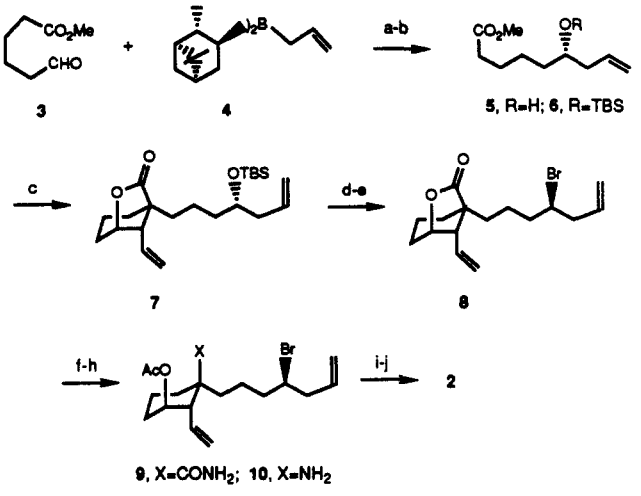
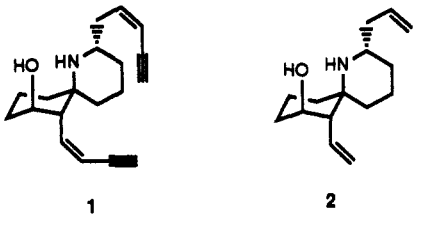
Histrionicotoxin (**1**), isolated from a family of brightly colored frogs, *Dendrobates histrionicus*,[1] found in Colombia, inhibits the function of several channels in electrogenic membranes.[2,3] Histrionicotoxin is a member of a family that revealed the first examples of an unusual class of spiropiperidine alkaloids bearing acetylenic, allenic, or olefinic side chains. Not surprisingly, this unique chemical constitution has been the target of considerable synthetic effort, but although much imaginative work has been directed toward the preparation of the relatively simple perhydro

**Scheme I.** Synthesis of Histrionicotoxin 235A[a]




[a] (a) −78 °C to room temperature, 2 h, 44%, 86% ee; (b) *t*-$BuMe_2SiCl$, imidazole, $CH_2Cl_2$, cat. DMAP, 2 days, 98%; (c) LDA, HMPA/THF (6:11 v/v), *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane, −78 °C to room temperature, 40 min, then LDA, −78 °C to room temperature, 2 h, 43%; (d) 5% HCl, THF, 12 h, 91%; (e) $Ph_3P$, $CBr_4$, ether, 2 h, 61%; (f) $NH_4Cl$, $AlMe_3$, PhH, 50 °C, 40 h; (g) $Ac_2O$, Py, DMAP, 56%; (h) $(CF_3CO_2)_2IPh$, $CH_3CN$, $H_2O$, 3 days; (i) $Et_3N$, $ClCH_2CH_2Cl$, 65–70 °C, 2 h, 40%; (j) MeOH, aqueous $Na_2CO_3$, 24 h, 78%.

derivative of histrionicotoxin,[2] only one group has accomplished the synthesis of (±)-histrionicotoxin itself.[4]




**1** **2**

We now report that the "allylic epoxide cyclization" method we recently disclosed[5] allows an efficient stereocontrolled path to this group of alkaloids, whether natural histrionicotoxin itself or simpler relatives. We illustrate this by the synthesis of (−)-histrionicotoxin 235A (**2**), in addition to that of the archetype of the group, (−)-histrionicotoxin (**1**).

We describe first the synthesis of the simpler (−)-histrionicotoxin 235A (Scheme I). This began with the optically active methyl (*S*)-6-hydroxy-8-nonenoate (**5**), readily accessible by the reaction of methyl 6-oxohexanoate (**3**)[6] and *B*-allyldiisopinocampheylborane (**4**)[7] (from (−)-α-pinene, 87% ee) in 86% ee and 44% yield. The *tert*-butyldimethylsilyl ether **6** of alcohol **5** was transformed, in a single operation (alkylation, using lithium diisopropylamide, with *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane[5] was followed by cyclization), to give lactone **7**, in which three chiral centers are correctly set for eventual transformation to (−)-histrionicotoxin. Removal of the silyl protecting group with dilute hydrochloric acid was followed by formation, with inversion, of the secondary bromide (triphenylphosphine–carbon tetrabromide) (**8**)[8] of the proper configuration for subsequent formation of the required piperidine ring. The construction of that ring now required conversion of the lactone carbonyl to an amino group: This was initiated by treatment of **8** with trimethylaluminum–ammonium chloride,[9] followed by acetic anhydride, to give the acetoxy amide

(1) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.
(2) For reviews: Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, p 1.
(3) Spivak, C. E.; Maleque, M. A.; Oliveria, A. C.; Masukawa, L.; Tokuyama, T.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *21*, 351.
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(5) Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 1661.
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(8) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

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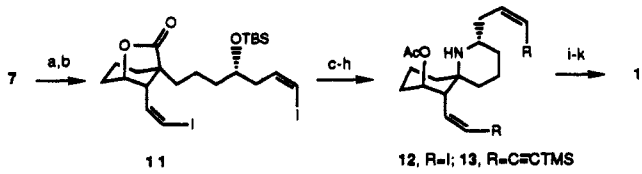
**Scheme II.** Synthesis of Histrionicotoxin[a]




[a] (a) $O_3$, then $Ph_3P$; (b) $(Ph_3P^+CH_2I)I^-$, $NaN(TMS)_2$, HMPA, THF, 52%; (c) 5% HCl, THF; (d) $Ph_3P$, $CBr_4$, ether, 2 h, 53%; $NH_4Cl$, $AlMe_3$, PhH, 40 °C, 18 h; (f) $Ac_2O$, Py, DMAP, 70%; (g) $(CF_3CO_2)_2IPh$, $CH_3CN$, $H_2O$, 3 days; (h) $Et_3N$, $ClCH_2CH_2Cl$, 65-70 °C, 2 h, 31% (A small quantity of the 2-epimer was undoubtedly formed in step d (cf. footnote 12) and was removed during the silica gel purification of **12**); (i) $Pd(PPh_3)_4$, CuI, PhH, (trimethylsilyl)-acetylene; (j) $Bu_4N^+F^-$; (k) aqueous $K_2CO_3$, MeOH, 40%.

9. Protection of the alcohol functionality was essential to prevent carbamate formation during the Hoffman-like rearrangement of amide **9** to amine **10**. The latter reaction could be accomplished satisfactorily by treatment of **9** with phenyliodonium bistrifluoroacetate in aqueous acetonitrile.[10] Cyclization of the amine **10** thus obtained was carried out at 55 °C with triethylamine in 1,2-dichloroethane to give, after deprotection, histrionicotoxin 235A (**2**) ($[\alpha]^{25}_D$ -102°, $c$ = 1.82, EtOH)[11,12] in 10 steps (1.8% overall yield) from the readily available ester **3**.

We considered first an approach to the synthesis of histrionicotoxin itself which simply involved elaboration of histrionicotoxin 235A. This approach was abandoned when it became clear that protection of the very hindered secondary amine was going to be very difficult: acylating agents, for instance, only acylated the secondary hydroxyl group. Another approach was abandoned when a known method for the introduction of a (*Z*)-enyne chain proved unsuitable.[13]

The successful route to histrionicotoxin involved the assumption that an effective assembly of the required (*Z*)-enyne system should result from the palladium-catalyzed coupling of a (*Z*)-vinyl iodide with a suitable derivative of acetylene. We further assumed that the vinyl iodide system would prove compatible with the chemical transformations that would have to follow its early introduction in a histrionicotoxin precursor. Both assumptions proved to be correct.

The most direct application of this strategy to the systems readily available to us required an effective method for the synthesis of (*Z*)-vinyl iodides from aldehydes. This problem, in fact, provided the motivation for designing the method we recently reported to achieve this transformation.[14] Its application to the dialdehyde obtained by ozonolysis of lactone **7**, itself an early intermediate on the route (vide supra) to histrionicotoxin 235A, successfully led to the bis((*Z*)-vinyl iodide) **11** (Scheme II). In a similar manner as described above for the synthesis of histrionicotoxin 235A, **11** was converted to the spiropiperidine **12**, which was then coupled with (trimethylsilyl)acetylene[15] to give the dienyne **13**. Deprotection of **13** proceeded smoothly to give (-)-histonicotoxin ($[\alpha]^{25}_D$ -114°, $c$ = 1.06, EtOH) (11 steps, 2.4% overall yield, from **7**). The spectroscopic data (IR, MS (CI), NMR) for the synthetic (-)-histrionicotoxin coincided with those obtained with authentic natural (-)-histrionicotoxin.

The two total syntheses just described are the first recorded syntheses of naturally occurring members of the histrionicotoxin family in the proper absolute stereochemistry. They illustrate important features of the "allylic epoxide cyclization": brevity, as well as regio-, stereo-, and enantioselectivity.

**Acknowledgment.** We thank Dr. J. W. Daly of the National Institutes of Health for a sample of natural (-)-histrionicotoxin, Dr. A. Srikrishna for his valuable studies of earlier routes to histrionicotoxin, and the National Science Foundation and the National Institutes of Health for their support.

(9) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(10) Boutin, R. H.; Loudon, G. M. *J. Org. Chem.* **1984**, *49*, 4277.
(11) Histrionicotoxin 235A has the following characteristics: IR ($CHCl_3$) 3681, 3601, 3350 (br), 3068, 3020, 2978, 2939, 2872, 1640, 1602, 1524, 1429, 1336, 1128, 1074, 995, 970, 923 $cm^{-1}$; MS (CI) 235 ($M^+$), 220, 218, 194, 192, 176, 166, 150, 110, 108, 96, 93, 85, 83; $^{13}C$ NMR (67.5 MHz; $CDCl_3$, 78.13) 137.3, 135.5, 119.0, 118.9, 73.97, 55.80, 50.92, 46.45, 42.34, 37.87, 37.49, 32.86, 29.41, 19.84, 16.28; $^1H$ NMR (400 MHz; $CHCl_3$, 7.27) $\delta$ 5.81 (dtq, $J$ = 0.8, 10, 7.6 Hz), 5.68 (ddt, $J$ = 0.8, 17, 10 Hz), 5.07-5.21 (m), 3.80 (m), 3.07 (m), 2.99 (d, $J$ = 10 Hz), 2.18 (dt, $J$ = 0.8, 6.8 Hz), 2.05 (qt, $J$ = 14, 4 Hz).
(12) Some 2-epihistrionicotoxin 235A (11%) was also obtained (eluted first from silica gel). This arises mainly from the 7% (*R*)-**5** formed in the enantioselective synthesis of **5** and possibly from a small amount of racemization in the formation of bromide **8**.
(13) The reaction of aldehyde **14** with the titanium tetraisopropoxide complex of the anion of bis(trimethylsilyl)propyne led to a 1:1 mixture of the *Z* and *E* olefins **15**, even though these are the same conditions that convert


cyclohexanecarboxaldehyde almost entirely to (*Z*)-1-cyclohexyl-4-(trimethylsilyl)-1-buten-3-yne, the correct geometric isomer in the context of histrionicotoxin synthesis. Cf.: Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.
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## Highly Efficient Asymmetric Hydrogenation of Amino Ketone Derivatives Leading to Practical Syntheses of (*S*)-Propranolol and Related Compounds†

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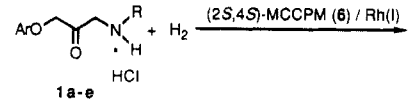
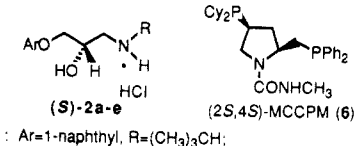
We report here an unprecedented and highly efficient asymmetric hydrogenation of the 3-(aryloxy)-2-oxo-1-propylamine derivatives **1a-e** leading to the practical synthesis of the (*S*)-1-amino-3-(aryloxy)-2-propanol derivatives **2a-e**, chiral β-adrenergic blocking agents, e.g., (*S*)-propranolol hydrochloride (**2a**).[1-3]




**2a** : Ar=1-naphthyl, R=$(CH_3)_3CH$; (*S*)-propranolol hydrochloride

The demonstrated synthesis of (*S*)-propranolol hydrochloride (**2a**) is shown in Scheme I. After conversion of 1-naphthol (**3**)

† Asymmetric Reactions Catalyzed by Chiral Metal Complexes. 41.
(1) For recently reported preparations of (*S*)-propranolol and related compounds by nonenzymatic asymmetric synthesis, see: (a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710. (b) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350. (c) Katsuki, T. *Tetrahedron Lett.* **1984**, *25*, 2821. (d) Bäckvall, J. E.; Björkman, E. E.; Bystrom, S. E. *Tetrahedron Lett.* **1982**, *23*, 943.
(2) For the synthesis of homochiral β-blockers utilizing enzyme technology, see: (a) Terao, Y.; Murata, M.; Achiwa, K.; Nishino, T.; Akamatsu, M.; Kamimura, M. *Tetrahedron Lett.* **1988**, *29*, 5173. (b) Matsuo, N.; Ohno, N. *Tetrahedron Lett.* **1985**, *26*, 5533. (c) Hamaguchi, S.; Hasegawa, J.; Kawaharada, H.; Watanabe, K. *Agric. Biol. Chem.* **1984**, *48*, 2055. (d) Iriuchijima, S.; Kojima, N. *Agric. Biol. Chem.* **1982**, *46*, 1153. (e) Iriuchijima, S.; Keiyu, A.; Kojima, N. *Agric. Biol. Chem.* **1982**, *46*, 1953.
(3) For the synthesis of homochiral β-blockers using chiral building blocks, e.g., D-mannitol, see: (a) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447 and references cited therein. (b) Bouzoubaa, M.; Leclerc, G.; Rakhit, S.; Andermann, G. *J. Med. Chem.* **1985**, *28*, 896.

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