First Total Synthesis of (+)-Allopumiliotoxin 339A. A Practical Entry to Dendrobatid Alkaloids of the Allopumiliotoxin Class

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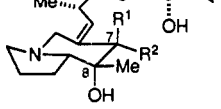
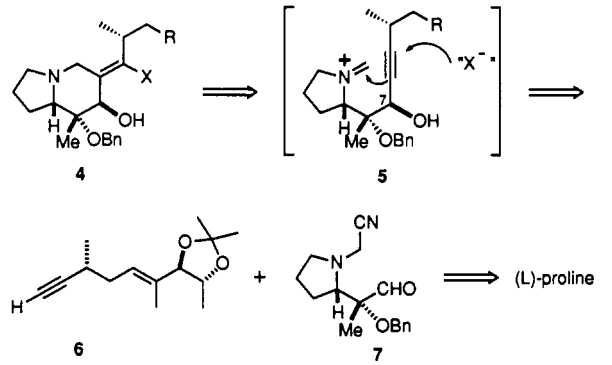
Several members of the pumiliotoxin A class of amphibian (Dendrobatidae) alkaloids display significant cardiotonic activity.[3-7] Recent pharmacological studies demonstrate that pumiliotoxin B (**3**) and certain congeners enhance sodium influx by binding to a unique modulatory site on the voltage-dependent sodium channel.[8,9] This interaction has been shown to stimulate phosphoinositide breakdown with the effect on this secondary messenger system being ultimately expressed as cardiotonic and myotonic activities. The allopumiliotoxins, which contain oxidation at both C(7) and C(8) of the indolizidine ring, are the most complex members of the pumiliotoxin A alkaloid group.[10] They are extremely rare in nature, and chemical synthesis is required to fully explore their biological activity. Allopumiliotoxins containing a β-oriented C(7) hydroxyl group display significantly greater biological activity than their α-epimers, with allopumiliotoxin 339A (**1**) being the only pumiliotoxin A alkaloid to be more effective than pumiliotoxin B in stimulating both sodium influx and phosphoinositide breakdown in guinea pig cerebral cortical synaptoneurosomes.[9] Two interesting total syntheses of the less active allopumiliotoxin 339B (**2**) have been recorded.[11,12] Unfortunately, neither synthetic route provides practical access to the allopumiliotoxin alkaloid class. In this paper we report the first total synthesis of (+)-allopumiliotoxin 339A. The directness and efficiency of this preparation establish the first practical synthetic route to the allopumiliotoxin alkaloids.



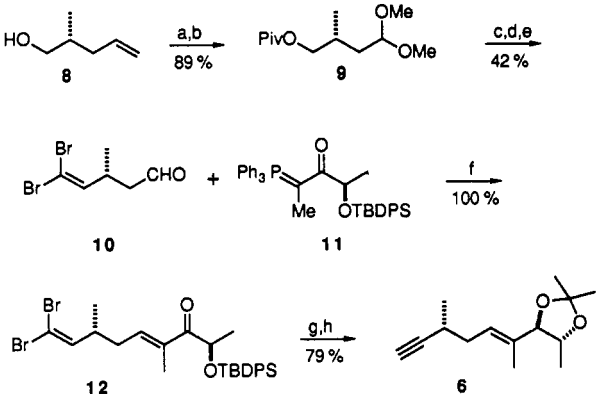
R^1	R^2	
OH	H	allopumiliotoxin 339A (**1**)
H	OH	allopumiliotoxin 339B (**2**)
H	H	pumiliotoxin B (**3**)

The convergent strategy we employed is summarized in Scheme I and involves the combination of the proline-derived aldehyde **7**[13] with the side-chain alkyne **6**. A central issue to be examined was the viability of the pivotal nucleophile-promoted iminium ion–alkyne cyclization step (**5** → **4**)[14] with a substrate that contained a potentially labile and inductively deactivating C(7) allylic hydroxyl group.

Scheme I



Scheme II. Synthesis of Side-Chain Alkyne[a]



[a] Piv = *t*-BuCO, TBDPS = *t*-BuPh$_2$Si. Reaction details: (a) PivCl, *i*-Pr$_2$NEt, 4-(dimethylamino)pyridine (cat.), CH_2Cl_2, 23 °C, 99%; (b) O_3, MeOH, −78 °C; Me_2S, −78 → 23 °C; TsOH (cat.), 23 °C, 90%, **9** $[\alpha]^{23}_D$ −3.7° (*c* 5.2, $CHCl_3$); (c) $LiAlH_4$, Et_2O, 0 °C, 85%; (d) Swern oxidation,[17] 81%; (e) Ph_3P, CBr_4, K_2CO_3, CH_2Cl_2, −78 °C; HBF_4 (25% aqueous, 2.4 equiv), THF, 23 °C, 62%, **10** $[\alpha]^{22}_D$ −22.8° (*c* 2.0, $CHCl_3$); (f) **11** (3 equiv), CH_2Cl_2, reflux, 100%; (g) (*i*-Bu)$_3$Al, pentane–toluene, 23 °C; (*n*-Bu)$_4$NF, THF, 23 °C, 100%; (h) TsOH (cat.), MeCOMe, 23 °C; *n*-BuLi (2.6 equiv), THF, −78 °C; NH_4Cl–H_2O, 79%, **6** $[\alpha]^{23}_D$ −10.1° (*c* 2.1, $CHCl_3$).

Alkyne **6** contains the full side chain of the pumiliotoxin A alkaloids **1–3**; a direct synthesis of this intermediate is summarized in Scheme II.[15] The preparation begins with (*R*)-2-methyl-4-pentenol, $[\alpha]^{23}_D$ +2.6° (*c* 1.5, $CHCl_3$), which is conveniently available by the Evans asymmetric alkylation procedure.[16] Conventional operations convert **8** to aldehyde **10**.[17,18] This intermediate is then condensed with the lactate-derived phosphorane **11** to give the α'-silyloxy (*E*)-enone **12** in essentially quantitative yield.[19,20] Reduction of **12** with (*i*-Bu)$_3$Al occurs with 11:1 facial selectivity to afford the *syn*-diol,[19,21] which is converted to the acetonide derivative. This intermediate is subsequently treated with excess *n*-BuLi followed by protonolysis to

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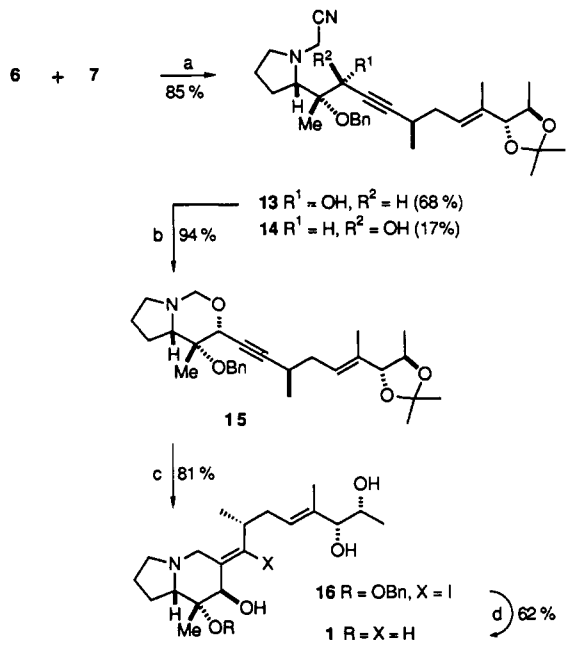
Scheme III. Synthesis of (+)-Allopumiliotoxin 339A[a]



[a] Bn = CH_2Ph. Reaction details: (a) **6** (1.3 equiv), *n*-BuLi (1.3 equiv), THF, −78 °C; **7**, −78 °C, 2.5 h, 85%; (b) $AgOSO_2CF_3$ (2.1 equiv), THF, 23 °C, 94%, **15** $[\alpha]^{22}_D$ −66.5° (*c* 2.2, $CHCl_3$); (c) TsOH (3 equiv), NaI (10 equiv), $(CH_2O)_n$ (5 equiv), 1:10 acetone–H_2O, 100 °C, 2 h, 81%; (d) *n*-BuLi (excess), THF, −78 → 23 °C; MeOH, 81%; Li (excess), NH_3, −78 °C, 3 min, 76%.

provide the desired (−)-alkyne **6** in 30% overall yield from alcohol **8**.

Addition of the alkynyllithium derivative of **6** to the α-benzyloxy aldehyde **7**[13] (THF, −78 °C) occurs in good yield with 4:1 selectivity (Scheme III). The sense of stereoselection was anticipated to arise from attack of the alkynyl nucleophile on the five-membered-ring lithium chelate of the carbonyl and ether oxygens of **7**. The resulting alcohol stereoisomers can be separated on silica gel to provide **13** and **14** in 68% and 17% yields, respectively. Although the corresponding alkynyldiisopropoxytitanium nucleophile[22] derived from **6** reacts with **7** with improved (>10:1) facial selectivity, the yield of this addition reaction is unacceptably low.[23] Treatment of **13** with AgOTf provides the cyclopentaoxazine **15** in high yield and sets the stage for the key cyclization step. Iodide-promoted cyclization of **15** occurs cleanly at 100 °C in acetone–H_2O in the presence of camphorsulfonic acid, with loss of the isopropylidene group, to afford alkylideneindolizidine **16** in 81% yield. No other stereoisomers were detected in the 500-MHz ^1H NMR spectrum of the cyclization product. Deiodination of **16**[14] followed by cleavage of the C(8) benzyl ether by careful treatment with Li–NH_3 at −78 °C provided (+)-allopumiliotoxin 339A (**1**) in 62% overall yield from **16**. Synthetic **1** was indistinguishable from an authentic sample[25] by TLC and 125-MHz ^{13}C NMR analysis. Of greatest significance, a 1:1 mixture of the synthetic and natural toxins is homogenous by 500-MHz ^1H NMR analysis in $CDCl_3$ and CD_3OD.[26] Synthetic (+)-allopumiliotoxin 339A shows optical rotations $[\alpha]^{23}_D$ +68.2° and $[\alpha]^{23}_{546}$ +90.0° (*c* 0.5, $CHCl_3$), while somewhat smaller rotations were measured for a small sample of the natural toxin: $[\alpha]^{22}_D$ +52.0° and $[\alpha]^{22}_{546}$ +75.0° (*c* 0.5, $CHCl_3$).

The most biologically active of the allopumiliotoxin A alkaloids, (+)-allopumiliotoxin 339A (**1**), has been prepared for the first time by total synthesis. The synthesis is reasonably direct and provides **1** in 16 steps and 15% overall yield from (*R*)-2-methyl-4-pentenol (**8**). The efficiency of the convergent strategy employed will for the first time allow practical access to natural and analogue allopumiliotoxins, thus greatly facilitating ongoing pharmacological studies in this area.

Acknowledgment. We thank the Heart and Lung Institute of the U.S. National Institutes of Health for their generous support (HL-25854). We particularly thank Dr. John Daly for a sample of natural (+)-allopumiliotoxin 339A and for his continued collaboration in the pumiliotoxin area. NMR and mass spectra were determined with instruments acquired with the assistance of NSF Shared Instrumentation grants.

Supplementary Material Available: Characterization data (IR, ^1H and ^{13}C NMR, [α], MS) for **10**, **12**, **6**, **13–16**, and **1** (5 pages). Ordering information is given on any current masthead page.

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(25) Kindly provided by Dr. John Daly.

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Structure of Centrally Bound *angular*-(Terphenylene)chromium Tricarbonyl

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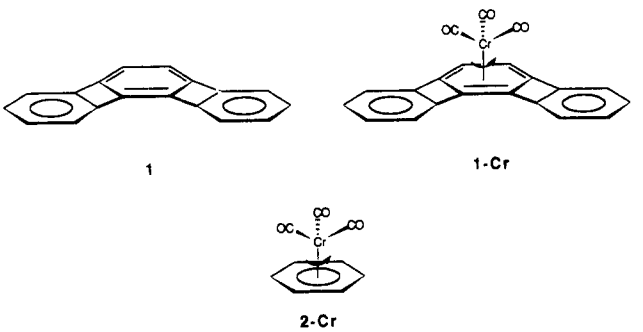
Conformational analysis, by extended Huckel methods, of the chromium tricarbonyl unit bound to cyclohexatriene and arenes with a dominant valence bond resonance form (e.g., naphthalene) reveals a *n*-octahedral geometry for the low-energy conformer.[2] The chromium tricarbonyl complex of *angular*-terphenylene (**1**) shows an unusually high barrier to rotation about the metal–arene bond.[3] This barrier and the chemical shifts of the ^{13}C carbonyl signals, under conditions of slow tripod rotation, support the assertion that **1**-Cr adopts an octahedral conformation in solution.



In the crystal structure of **1**-Cr[4] (Figure 1), the chromium

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