peaks might result from a number of mechanisms involving permutations of J-coupling interactions. Cross peaks between the ^{13}C resonances at 124.8 and 148.05 ppm and the *tert*-butyl ^1H resonance identify these as the C-3 and C-4 resonances, respectively. The former cross peak might arise from an initial ROESY transfer from the *tert*-butyl protons to H-3, followed by heteronuclear TOCSY transfer from H-3 to C-3 via one-bond coupling. The latter cross peak might arise from an initial ROESY transfer from the *tert*-butyl protons to H-3, followed by heteronuclear TOCSY transfer from H-3 to C-4 via long-range coupling ($^2J_{H3-C4} \approx 7.0$ Hz).[16] These cross peaks were not detected in other experiments which rely on development of coherence through J coupling in the laboratory frame.

HSL provides a valuable means of obtaining long-range structural information in high molecular weight molecules and promises to be an effective means of reducing the problems of rapid CSA relaxation encountered on very high field NMR spectrometers.

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Highly Stereocontrolled Total Synthesis of (+)-Allopumiliotoxin 339A

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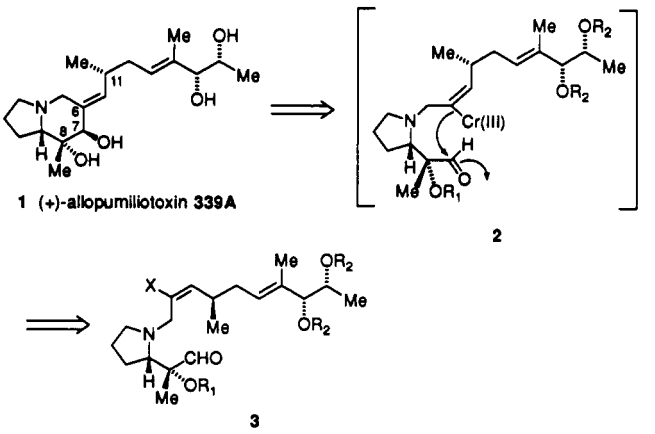
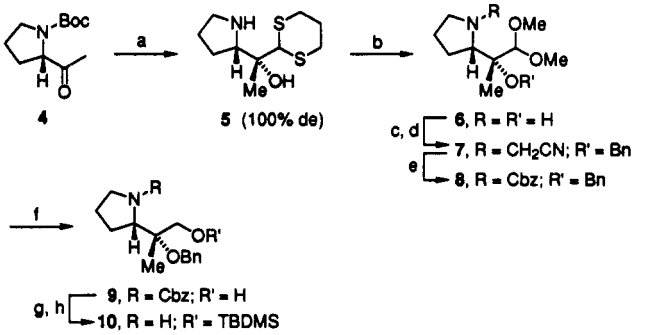
The dendrobatid alkaloids of the allopumiliotoxin A class, a series of the naturally occurring 7-hydroxy congeners of the pumiliotoxin A class, are one of the most structurally complex indolizidines produced in nature.[1] The distinct chemical structure and the significant biological activities of this class of alkaloids[2] have provided the stimulus for development of new methodologies for their syntheses, and two successful approaches to allopumiliotoxins 267A and 339B have been reported by Overman et al.[3a] and Trost et al.[3b] Recently, the first total synthesis of (+)-allopumiliotoxin 339A (**1**), isolated as a minor constituent from skin extracts of a family of Panamanian poison frogs, *Dendrobates auratus*,[4] has been published by Overman's group.[5]

In this communication we report a highly stereocontrolled approach to the synthesis of **1**, which provides an efficient, novel entry to the allopumiliotoxin A alkaloids. Such an approach is based upon intramolecular cyclization of **3** (X = halogen) for the formation of **1** involving direct construction of the 6-(*E*)-alkylideneindolizidine ring system as well as establishing the trans-diaxial 7,8-diol on the indolizidine ring as shown in Scheme I. We envisioned that this process would exploit the intramolecular Cr(II)-mediated coupling reaction[6] originally studied by Nozaki and co-workers,[7] wherein the cyclization would proceed via an alkenylchromium(III) species **2**.

Scheme I

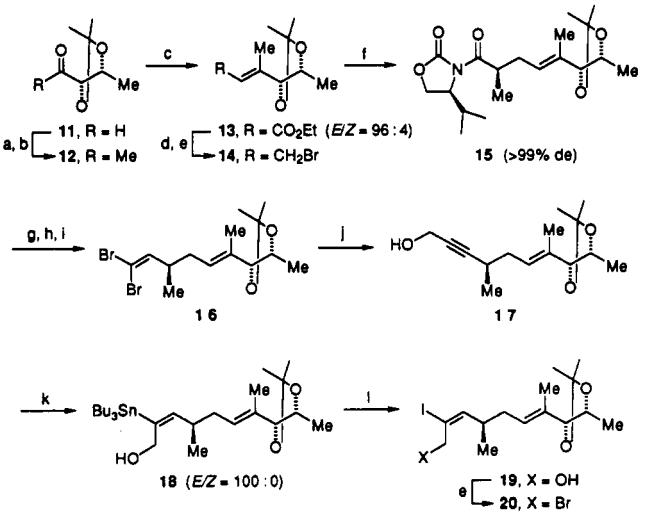


Scheme II[a]



[a] (a) CF_3CO_2H (3 equiv), CH_2Cl_2, room temperature, then 1,3-dithiane (5 equiv), BuLi (5 equiv), THF, −78 °C; (b) MeOH, $Hg(ClO_4)_2 \cdot xH_2O$, $CHCl_3$, room temperature; (c) ICH_2CN, Et_3N, THF, room temperature; (d) BnBr, KH, THF, reflux; (e) $AgNO_3$, EtOH, room temperature, then CbzCl, Et_3N, CH_2Cl_2, room temperature; (f) 3 N HCl, THF, room temperature, then $NaBH_4$, MeOH, room temperature; (g) *t*-$BuMe_2SiCl$, imidazole, DMF, room temperature; (h) H_2, 10% Pd/C, MeOH.

Scheme III[a]



[a] (a) MeMgBr, THF, 0 °C; (b) PCC, CH_2Cl_2, room temperature; (c) $(i\text{-}PrO)_2P(O)CH_2CO_2Et$, NaH, benzene, room temperature; (d) DIBALH, CH_2Cl_2/hexane, −78 °C; (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (f) (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone, LDA, THF, 0 °C; (g) $LiAlH_4$, THF, 0 °C; (h) DMSO, $(COCl)_2$, Et_3N, −78 °C; (i) CBr_4 (2 equiv), PPh_3 (4 equiv), CH_2Cl_2, 0 °C; (j) $(CH_2O)_n$, BuLi (2 equiv), THF, room temperature; (k) Bu_3SnH, $PdCl_2(PPh_3)_2$ (2 mol %), THF, room temperature; (l) I_2, CH_2Cl_2, room temperature.

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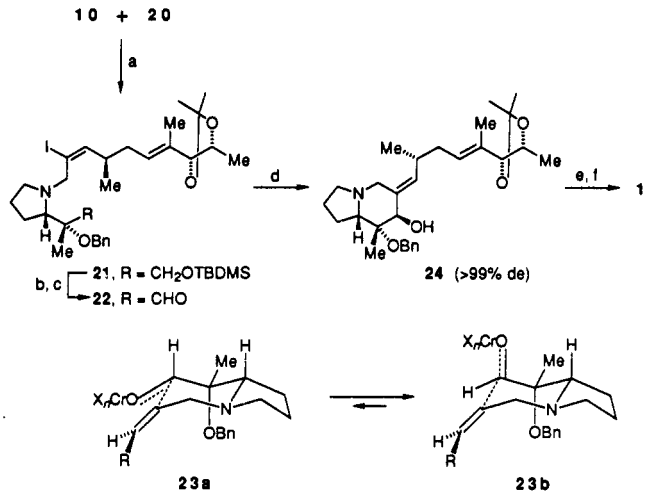
Scheme IV[a]



[a] (a) *i*-Pr_2NEt, THF, room temperature; (b) Bu_4NF, THF, room temperature; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (d) $CrCl_2$ (5 equiv), $NiCl_2$ (2.5 mol %), DMF, room temperature; (e) 3 N HCl/THF, room temperature; (f) Li, NH_3/THF, −78 °C.

The synthesis of the optically active pyrrolidine fragment is shown in Scheme II. Deprotection of *N*-Boc-protected (*S*)-2-acetylpyrrolidine **4** with trifluoroacetic acid (3 equiv) by the known procedure[3] afforded the pyrrolidine trifluoroacetate salt, which was immediately treated with excess 2-lithio-1,3-dithiane to produce the tertiary alcohol **5** (54% from **4**) as a single diastereomer consistent with a chelation-controlled transition state. Compound **5** was converted to **6** (68%) via transformation of the cyclic dithioacetal into the corresponding dimethyl acetal with methanol and $Hg(ClO_4)_2$. After blocking of the amino group by the cyanomethyl group,[8] O-benzylation of the tertiary alcohol was effected by treating with benzyl bromide and KH[9] to produce **7** (81%), which was then converted to the carbamate **8** (75%) via deblocking of the cyanomethyl group ($AgNO_3$) and N-protection by the Cbz group. Compound **8** was further transformed into **9** (97%) through acetal hydrolysis and $NaBH_4$ reduction of the resulting aldehyde. Silylation of **9** and hydrogenolytic removal of the Cbz group resulted in **10** (80% from **9**).

The side chain segment **20** was elaborated from the D-4-deoxythreose derivative **11**[10] as outlined in Scheme III. Grignard reaction (MeMgBr, THF) followed by PCC oxidation provided the methyl ketone **12** (73% overall yield), which was transformed to the *E* olefin **13** (84%) by Horner–Emmons condensation with a nice *E*:*Z* ratio of 96:4. The bromide **14**, obtained from **13** (DIBALH, then CBr_4/PPh_3) in 91% yield, was subjected to C_2 homologation based on Evans alkylation,[11] which provided **15** (83%) with virtually complete diastereoselective creation of the *R* stereogenic center at C-11. Reductive removal of the oxazolidine auxiliary on **15** with $LiAlH_4$, followed by Swern oxidation and treatment of the resultant aldehyde with CBr_4/PPh_3, furnished the dibromide **16** in 70% overall yield from **15**. Compound **16** was converted to the hydroxyalkyne **17** in 92% yield by treatment with BuLi (2 equiv) and paraformaldehyde. Palladium-catalyzed hydrostannation [Bu_3SnH, 2 mol % $PdCl_2(PPh_3)_2$, room temperature][12] of **17** provided full stereocontrol for the (tributylstannyl)alkene **18** (93%)[13] with correct *E* olefin geometry.[14] Upon exposure of **18** to iodine (CH_2Cl_2, room temperature), iododestannylation smoothly proceeded to give exclusively the (*E*)-iodoalkene **19**, which was then converted to the allylic bromide **20** in excellent yield (96% from **18**).

Construction of the alkylideneindolizidine ring began with coupling of **10** and **20** in the presence of Hünig base to provide **21** in 70% yield (Scheme IV). Desilylation of **21** followed by Swern oxidation afforded the aldehyde **22** (81%). Intramolecular cyclization of **22** was successfully achieved by application of mild coupling conditions (5 equiv of $CrCl_2$, 2.5 mol % $NiCl_2$, DMF, room temperature) with virtually complete stereocontrol, giving rise to **24** in 79% yield. This cyclization through the alkenylchromium(III) intermediate (**2** in Scheme I) generated with Ni(II) catalyst via transmetalation led to both formation of the 6-(*E*)-alkylideneindolizidine and introduction of the axial 7β-hydroxy group at the same time in *a single operation*. The remarkably high degree of stereoselectivity leading to **24** may be explained by examination of two chair-like transition states, **23a** and **23b**, the former of which would be destabilized owing to an allylic 1,3-strain[15] between the equatorial chromium alkoxide and the olefin. The preferred transition state **23b** leads to the requisite axial 7-hydroxy group.

Finally, sequential removal of the isopropylidene protecting group (3 N HCl, THF) and the benzyl group (Li, NH_3/THF) provided (+)-allopumiliotoxin 339A (**1**) in 71% overall yield. Synthetic **1** had $[\alpha]^{28}_D$ +38.8° (*c* 0.5, MeOH) [lit.[4] $[\alpha]^{25}_D$ +29.4° (*c* 1.0, MeOH)], $[\alpha]^{28}_D$ +72.4° (*c* 0.66, $CHCl_3$) [lit.[5] $[\alpha]^{23}_D$ +68.2° (*c* 0.5, $CHCl_3$)] and exhibited spectral data (^1H and ^{13}C NMR) identical with those reported[4] for the natural product.

In conclusion, a new, highly regio- and stereocontrolled approach for the synthesis of allopumiliotoxin 339A has been developed. Our methodology based on an intramolecular chromium(II)-mediated cyclization should prove an efficient tool in the synthesis of the allo series of pumiliotoxins.

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Dynamic Interpretation of NMR Data: Molecular Dynamics with Weighted Time-Averaged Restraints and Ensemble *R*-Factor

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Determination of biomolecular structure in solution via multidimensional NMR and modeling with distance geometry and restrained molecular dynamics (rMD) generally results in a single structure in accord with structural constraints, i.e., interproton distances extracted from nuclear Overhauser enhancement (NOE) spectra and torsion angles arising from coupling constants. With rapid conformational fluctuations, constraints are time-averaged, with the time scale and nonlinear averaging being different for torsion angles and distances. Conceivably then, there is no single energetically reasonable structure that would fit all structural data simultaneously as demonstrated for the peptide antamanide.[1] A

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