Total Synthesis of Pumiliotoxins A and 225F

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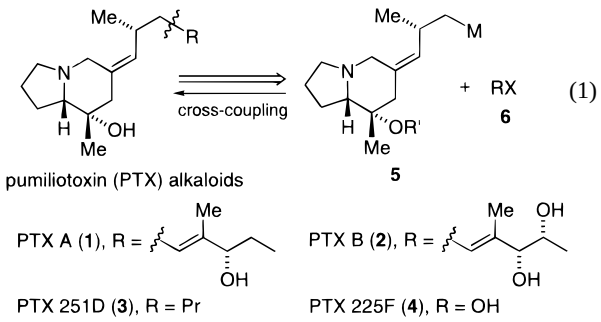
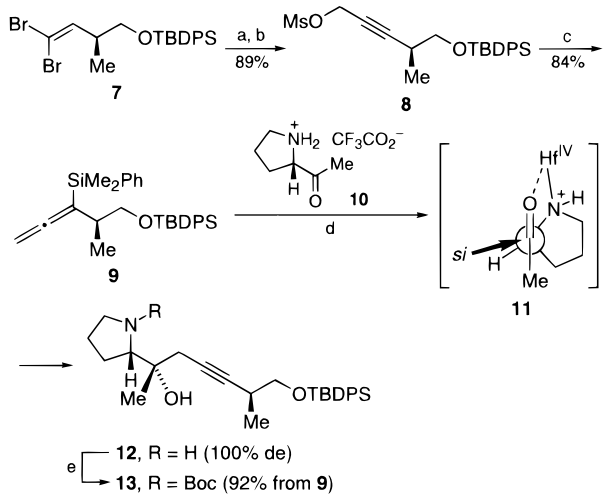
A number of the amphibian alkaloids[1] structurally related to pumiliotoxin (PTX) A (**1**) and B (**2**), now totaling almost 30, are grouped into a subclass called pumiliotoxins[1a] which are all characterized structurally by a (*Z*)-alkylideneindolizidine ring system differing in only the alkylidene side chain.[2] For the synthesis of these alkaloids, one significant challenge is the stereoselective incorporation of the (*Z*)-alkylidene side chain at C-6 of the indolizidine nucleus. In the search for control of the exocyclic alkene geometry as well as the piperidine ring construction, comprehensive efforts by the Overman group[3] have led to the development of the general methods for the syntheses of the pumiliotoxin alkaloids via two fundamental approaches based on iminium ion cyclization. After these brilliant and extensive studies and subsequent synthesis of pumiliotoxin 251D (**3**) by Gallagher and co-workers,[4] culminating in the total syntheses of pumiliotoxins A (**1**), B (**2**), and 251D (**3**), no further synthetic approach has appeared. In this paper, we wish to disclose a general approach for preparing the pumiliotoxin alkaloids, which led to asymmetric total synthesis of pumiliotoxins A (**1**)[5] and 225F (**4**); the latter synthesis is the first reported.

Since the common structural motif shared by all the pumiliotoxin alkaloids is the presence of the (*Z*)-alkylideneindolizidine fraction, the strategic disconnection of the pumiliotoxin alkaloids at the C-12−C-13 bond of the alkylidene side chain (indicated by the wavy line in eq 1) should be most appropriate for the



efficient and flexible synthesis of pumiliotoxin alkaloids. This bond would be formed by cross-coupling reaction between a metal derivative **5** of the (*Z*)-alkylideneindolizidine fraction and the vinyl or alkyl halides **6**. Our first efforts were thus directed toward the development of stereoselective construction of the (*Z*)-alkylideneindolizidine component as a pivotal common precursor.

Scheme 1[a]



[a] Reagents and conditions: (a) BuLi, $(CH_2O)_n$, THF, −78 → 0 °C; (b) MsCl, Et_3N, CH_2Cl_2, −30 °C; (c) $(Me_2PhSi)_2Cu(CN)Li_2$, THF, −85 °C, 3 min; (d) $HfCl_4$, CH_2Cl_2, −78 → 0 °C; (e) $(Boc)_2O$, K_2CO_3.

The dibromoolefin **7**[6] was converted to the homopropargyl mesylate **8** by treatment with BuLi and paraformaldehyde followed by mesylation (Scheme 1). Conversion of **8** to the allenylsilane **9** was successfully achieved in 84% yield by using the bis(dimethylphenylsilyl)cuprate reagent according to Fleming's method.[7] Lewis acid-mediated nucleophilic addition[8] of the allenylsilane **9** to the trifluoroacetate salt of (*S*)-2-acetylpyrrolidine (**10**)[9] proceeded cleanly by using hafnium(IV) chloride to afford the desired homopropargylic alcohol **12**, which was isolated as the N-Boc derivative **13**, with complete stereocontrol in excellent overall yield (92%). The stereochemical outcome of this $HfCl_4$-promoted propargylation can be interpreted in terms of a Cram chelate transition-state model **11**.[10]

Radical-initiated hydrostannylation of **13** using triethylborane and triphenyltin hydride proceeded with complete trans selectivity to give the (*Z*)-3′-stannylalkene **14** (60%) along with the (*Z*)-4′-stannyl regioisomer (28%) (Scheme 2). The assignment of the *Z* stereochemistry of **14** was made on the basis of the large coupling constant (89.3 Hz) between Sn and the vinyl proton.[11] Upon treatment with *N*-iodosuccinimide, **14** underwent iododestannylation with retention of the *Z* configuration to afford the vinyl iodide **15**. Palladium-catalyzed carbonylation[12] of **15** smoothly occurred when treated with carbon monooxide and tributylamine in the presence of a catalytic amount of $Pd(OAc)_2$ (2 mol %) and PPh_3 (8 mol %) in HMPA at 100 °C,[13] furnishing the lactone **16** in 97% yield. Deprotection of **16** followed by DIBAL reduction gave the diol **17**, which underwent smooth intramolecular cyclodehydration[14] with carbon tetrabromide and PPh_3 to form

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(4) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

(5) For total syntheses of pumiliotoxin A, see: (a) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669. (b) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901. (c) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

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(8) For the $TiCl_4$-mediated addition of allenylsilanes to carbonyl compounds, see: (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870.

(9) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179.

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(11) In our earlier study, smaller coupling constants (ca. 35 Hz) have been observed for (*E*)-stannyl alkenes prepared by syn selective palladium-catalyzed hydrostannylation. See: Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393.

(12) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(13) Procedure according to Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684.

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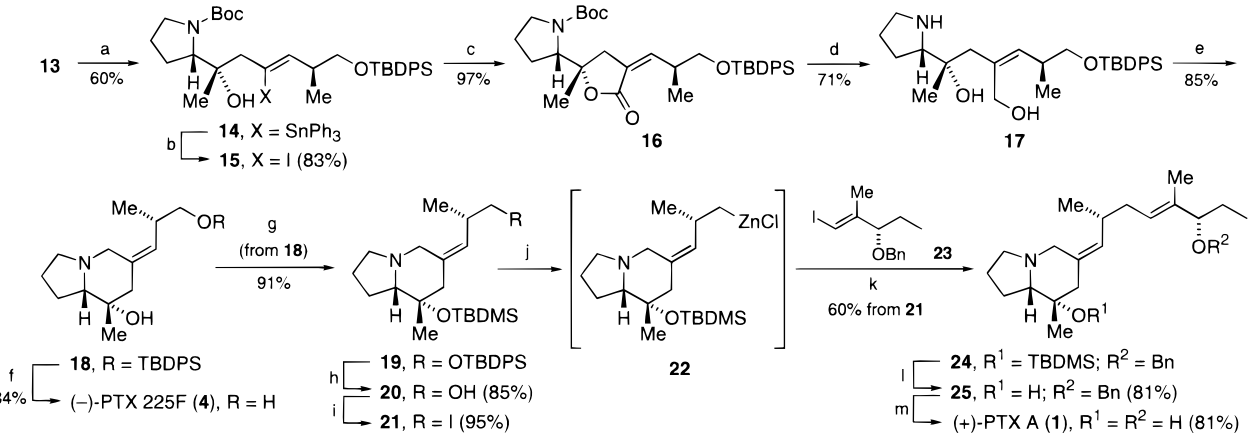
Scheme 2[a]



[a] Reagents and conditions: (a) Ph_3SnH, Et_3B, benzene, 5 days; (b) NIS, CH_2Cl_2, 0 °C; (c) CO, $Pd(OAc)_2$ (2 mol %), PPh_3 (8 mol %), Bu_3N, HMPA, 100 °C; (d) (i) CF_3CO_2H, CH_2Cl_2, 0 °C; (ii) DIBALH, toluene, −30 °C; (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min; (f) Bu_4NF, THF; (g) TBDMSOTf, 2,6-lutidine, DMAP, CH_2Cl_2, 0 °C; (h) $(Me_2N)_3S(Me_3SiF_2)$ (1.5 equiv), DMF; (i) I_2, PPh_3, imidazole, CH_2Cl_2; (j) (i) *t*-BuLi, Et_2O, −110 °C; (ii) $ZnCl_2$, THF, −78 → 0 °C; (k) $Pd(PPh_3)_4$ (13 mol %), benzene; (l) Bu_4NF, DMF, 60 °C; (m) Li, NH_3−THF, MeOH, −78 °C.

the (*Z*)-alkylideneindolizidine **18** in 85% yield. Subsequent treatment of **18** with Bu_4NF resulted in the first total synthesis of (−)-pumiliotoxin 225F (**4**). The synthetic material displayed spectral properties (^{13}C NMR and MS) that matched those of the natural product.[15] However, the observed rotation of synthetic **4** ($[\alpha]^{24}_D$ −25.3 (*c* 0.25, $CHCl_3$)) was found to be significantly lower than the reported value[15] ($[\alpha]_D$ −87.4 (*c* 0.23, $CHCl_3$)). The reason for this discrepancy in the optical rotations is unclear at present, although it might be attributed to the contamination of a small amount of a highly optically active impurity in the natural sample.

For the formation of the (*Z*)-alkylideneindolizidine metal species **5** (led by the illustrated disconnection in eq 1) as the coupling partner, **18** was protected as the TBDMS ether **19**, and the selective deprotection of the primary TBDPS ether was performed using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)[16] to provide the primary alcohol **20** (85%), which was then converted to the iodide **21** (95%).

We thus completed the stereoselective construction of **21** possessing a common fundamental structural unit of the pumiliotoxin alkaloids, and the stage was then set for the critical cross-coupling reaction with the chiral (*E*)-vinyl iodide **23** for the synthesis of pumiliotoxin A (**1**). One potential problem associated with the transition metal-catalyzed homoallyl−alkenyl coupling would be the tendency of the homoallylic compounds to undergo *β*-elimination. This problem was overcome by Negishi,[17] who adapted homoallylic organozincs to the palladium-catalyzed conjugate substitution reaction with alkenyl halides to effect the construction of 1,5-dienes. In view of these results, we explored the use of the organozinc for the cross-coupling reaction.[18] Thus, the homoallyl iodide **21** was subjected to halogen−metal exchange with *tert*-butyllithium at −110 °C, followed by transmetalation with $ZnCl_2$. Subsequent one-pot treatment of the resulting homoallylzinc reagent **22** with the chiral (*E*)-vinyl iodide **23**[19] in the presence of catalytic $Pd(PPh_3)_4$ afforded the cross-coupled product **24** in 60% yield from **21** with complete retention of configuration of the stereocenter(s) and (*Z*)-geometry. Finally, removal of the TBDMS protecting group gave **25** ($[\alpha]^{22}_D$ −2.7 (*c* 0.59, $CHCl_3$) [lit.[5a] $[\alpha]^{25}_D$ −2.1 (*c* 0.70, $CHCl_3$)] (66% or 81% based on 18% recovery of **24**), which was subjected to benzyl ether cleavage through the Overman protocol[5a] (Li, NH_3, MeOH) to provide (+)-pumiliotoxin A (**1**) ($[\alpha]^{25}_D$ +16.7 (*c* 0.84, $CHCl_3$) [lit.[5a] $[\alpha]^{23}_D$ +14.9 (*c* 0.65, $CHCl_3$)] in 81% yield. The ^1H and ^{13}C NMR data of synthetic **1** were identical with those of natural pumiliotoxin A (307A′).[20]

The new strategy developed herein has served to demonstrate the potential of the homoallyl−alkenyl coupling protocol for a general entry to the convergent asymmetric synthesis of the pumiliotoxin alkaloids. It relies on a palladium(0)-based cross-coupling reaction employing a novel, complex homoallylzinc molecule with a nitrogen heterocycle, which is, to the best of our knowledge, the first example of the application of such a reaction in natural product synthesis.[21,22] Studies to extend this methodology to other pumiliotoxin alkaloids are in progress.

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Supporting Information Available: Spectroscopic data for compounds **1**, **4**, **9**, **13**−**21**, **24**, and **25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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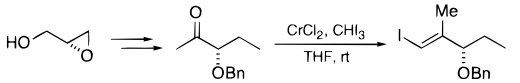

23 (*E*/*Z* = 89:11)

(20) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183.

(21) Only a limited number of applications of the homoallyl−alkenyl coupling strategy using functionalized nonnitrogenous homoallylic zinc species in natural product synthesis have been published. See ref 17 and also: William, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198.

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