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Journal of Organometallic Chemistry 653 (2002) 229–233

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

A convergent total synthesis of pumiliotoxins A and B via palladium-catalyzed cross-coupling reaction of homoallylic organozinc compounds with vinyl iodides

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Received 5 September 2001; received in revised form 26 November 2001; accepted 28 November 2001

Abstract

A versatile convergent approach for preparing the pumiliotoxin alkaloids has been developed employing a Pd(0)-catalyzed cross-coupling reaction between homoallylic organozincs and vinyl iodides, which led to the asymmetric total synthesis of (+)-pumiliotoxins A (**1**) and B (**2**). The (*Z*)-alkylideneindolizidine, which is a common organic part of the organozinc reagents in this approach, was synthesized with a high degree of stereocontrol upon using $HfCl_4$-mediated addition of the allenylsilane to (*S*)-2-acetylpyrrolidine. The (*Z*)-iodoalkylideneindolizidine (**31**) thus obtained as an advanced common intermediate was converted into the homoallylzinc chloride derivative **32**, which underwent homoallyl-vinyl cross-coupling with the (*E*)-vinyl iodide (**13**) using $Pd(PPh_3)_4$ catalyst to afford the 1,5-diene product **33**. Subsequent deprotection provided (+)-pumiliotoxin A. On the other hand, **31** was transformed into the homoallyl-*tert*-butyl zinc intermediate **39**, which was cross-coupled with the (*E*)-vinyl iodide (**36**) in the presence of the Pd(0) catalyst. The resulting 1,5-diene product **40** underwent subsequent deprotection to afford (+)-pumiliotoxin B. © 2002 Published by Elsevier Science B.V.

Keywords: Palladium-catalyzed cross-coupling reaction; Homoallylzincs; Vinyl iodides; Alkylideneindolizidines; (+)-Pumiliotoxins A and B

1. Introduction

Neotropical poison-dart frogs of the family Dendrobatidae have been a rich source of various structurally unique and biologically significant alkaloids [1]. Among these natural products, pumiliotoxins A (**1**) and B (**2**), isolated as the major toxic alkaloids from skin extracts of the Panamanian poison frog *Dendrobates pumilio* in 1967 [2], were the first representatives of the pumiliotoxin class of dendrobatid alkaloids. This class of alkaloids closely related to pumiliotoxins A and B, now totaling over 20 [1d], is all characterized structurally by a (*Z*)-6-alkylidene-8-hydroxy-8-mehtylindolizidine ring system differing in only the alkylidene side chain [1]. These alkaloids have shown to have modulatory effects on voltage-dependent sodium channels, therefore, displaying in some cases potent cardiotonic and myotonic activity [3].

The selective generation of *E*- and *Z*-*exo*-cyclic olefins has traditionally been attained via π-bond construction employing the Wittig reaction or aldol condensation, however, these methods have been less than satisfactory. In this regard, stereodefined generation of the (*Z*)-alkylidene side chain at C-6 of the indolizidine nucleus is one significant challenge in the synthesis of the pumiliotoxin class of alkaloids. In the search for control of the *exo*-cyclic alkene geometry as well as the piperidine ring construction, comprehensive efforts were made by the Overman group [4] and have led to the development of the total synthesis of pumiliotoxins A, B, and 251D. After these pioneering studies and subsequent synthesis of pumiliotoxin 251D by Gallagher and co-workers [5], however, no further synthetic approach to the total synthesis of the pumiliotoxin alkaloids has appeared. Our own approach to the structural problem presented by this class of molecules has thus been to focus on the development of efficient construction of the (*Z*)-alkylideneindolizidine as a common intermediate and subsequent elaboration of a variety of the side chains based on a

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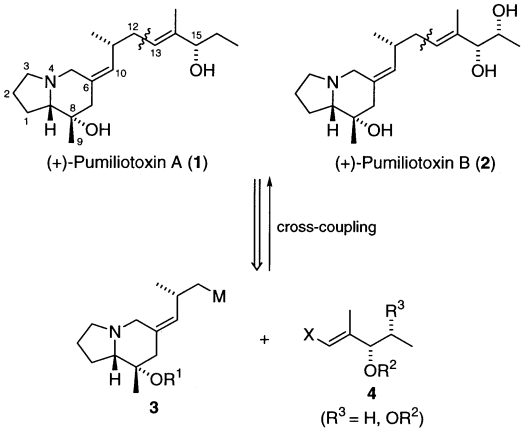
0022-328X/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0022-328X(02)01160-9

palladium-catalyzed cross-coupling reaction which is relevant to a convergent entry to the total synthesis of pumiliotoxins A (**1**) and B (**2**) [6].

2. Synthetic strategy

Since the presence of the (*Z*)-alkylideneindolizidine fraction is the common structural motif shared by not only pumiliotoxins A (**1**) and B (**2**) but also all other pumiliotoxin alkaloids, the strategic disconnection of the pumiliotoxin alkaloids at the C-12–C-13 bond of the alkylidene side chain should be most appropriate for the efficient and flexible synthesis of the pumiliotoxin class of alkaloids (Scheme 1). Our synthetic plan thus called for connecting these two fragments, the (*Z*)-alkylideneindolizidine (**3**) and the alkenyl halides (**4**). This approach allows for utilization of **3** as a common fragment, and which also allows for a convergent entry into the pumiliotoxin alkaloids. The central feature of this approach involving the construction of the homoallyl–alkenyl bond relies on the palladium(0)-based cross-coupling strategy. 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 [7], who subjected homoallylic organozincs to the palladium-catalyzed conjugate substitution reaction with alkenyl halides to effect the construction of 1,5-dienes. We envisioned that this coupling chemistry associated with the organozincs effects the combination of **3** and **4**, which would proceed via a catalytic cycle involving oxidative addition–transmetalation–reductive elimination sequence as depicted in Fig. 1, [8]. The critical homoallyl–alkenyl coupling process between the alkenyl iodide **5** and the homoallylzinc **7** would proceed with complete retention of configuration for the alkenyl iodide yielding the 1,5-diene unit **9**, which was expected to be adopted for assembling of the alkylidene side chains of pumiliotoxins A and B.



Scheme 1.

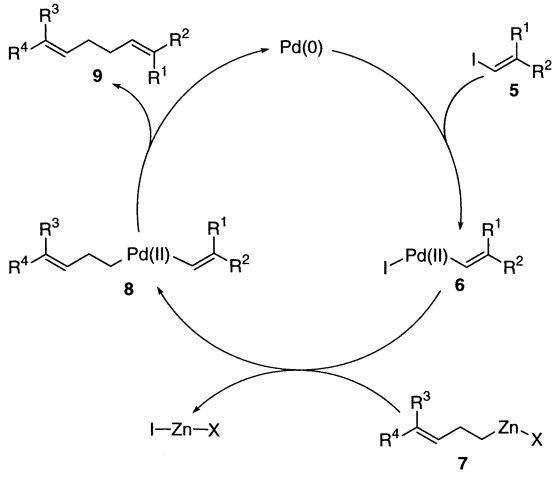
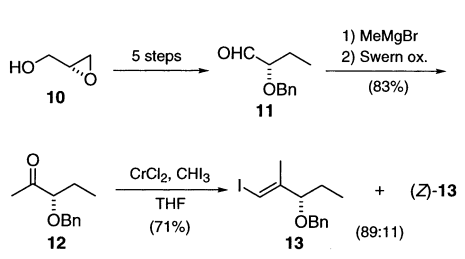


Fig. 1. Catalytic cycle for alkenyl–homoallyl cross-coupling.



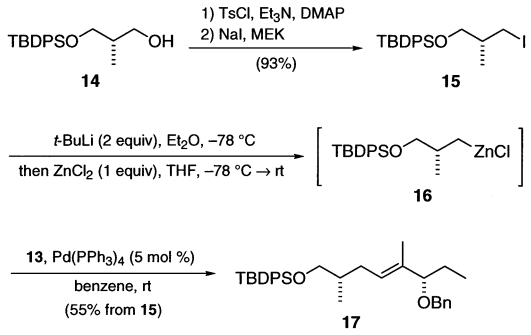
Scheme 2.

3. Total synthesis of (+)-pumiliotoxin A

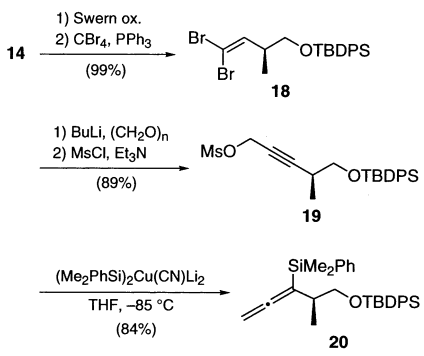
3.1. Preliminary experiments on the cross-coupling reaction

According to the above discussion, the synthesis started with the preparation of the vinyl iodide coupling partner **13** in homochiral form needed for the synthesis of (+)-pumiliotoxin A (**1**). Thus, (*R*)-glycidol (**10**) was converted to the ketone (**12**) in seven steps, and subsequent iodo-olefination was carried out using the Takai protocol [9] of treatment with $CrCl_2$ and iodoform to produce a chromatographically separable mixture (71% yield) of the (*E*)-vinyl iodide **13** and the (*Z*)-isomer in an 89:11 ratio favoring the desired (*E*)-isomer (Scheme 2).

Preliminary experiments were performed in order to determine the feasibility of **13** as the coupling partner in the Pd(0)-catalyzed cross-coupling reaction with the organozinc compound. Hence, the iodide **15**, prepared from the alcohol **14** with standard procedures, underwent halogen–metal exchange with two equivalents of *t*-BuLi at −78 °C, followed by transmetalation with one equivalent of $ZnCl_2$. Subsequent one-pot treatment



Scheme 3.



Scheme 4.

of the resulting alkylzinc reagent **16** with **13** in the presence of catalytic $Pd(PPh_3)_4$ led to the cross-coupled product **17** in 55% yield with complete retention of the (*E*)-geometry (Scheme 3).

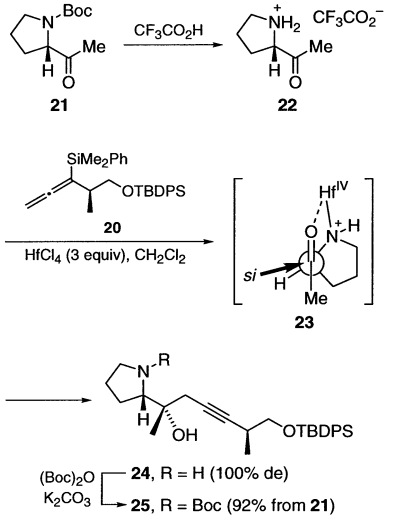
3.2. Preparation of the (*Z*)-iodoalkylideneindolizidine (*31*)

On the basis of these results, we next envisioned extending the cross-coupling strategy to the preparation of pumiliotoxin A (**1**) utilizing combination of the homoallylic zinc species of the (*Z*)-alkylideneindolizidine (**32** in Scheme 7) and the vinyl iodide **13**. With this approach in mind, we investigated the synthesis of the (*Z*)-iodoalkylideneindolizidine (**31**) needed for the preparation of the corresponding zinc reagent (**32**). The synthesis began with the above-described chiral alcohol (**14**), which was converted to the dibromoolefin (**18**) as shown in Scheme 4, Treatment of **18** with BuLi and paraformaldehyde followed by mesylation gave the homopropargyl mesylate (**19**), which was then converted to the allenylsilane (**20**) by using the bis(-dimethylphenylsilyl)cuprate reagent according to Fleming's method [10]. Lewis acid-induced nucleophilic addition [11] of **20** to the trifluoroacetate salt (**22**) of (*S*)-2-acetylpyrrolidine [12] proceeded cleanly by using hafnium(IV) chloride to afford the desired homopropargylic alcohol (**24**), which was isolated as the N-Boc derivative **25**, with complete stereocontrol in excellent overall yield (92%). The stereochemical outcome of the preferential formation of **24** in this $HfCl_4$-promoted propargylation can be accounted for by the transition-state model **23** involving the chelation of the NH and carbonyl groups with Hf (Scheme 5).

Radical-initiated hydrostannylation of **25** proceeded with complete *trans* selectivity to give the pure (*Z*)-3′-stannyl alkene 26 (60%) after chromatographic separation from the (*Z*)-4′-stannyl regioisomer (28%) (Scheme 6). Upon treatment with *N*-iodosuccinimide (**26**) underwent iodolysis with retention of the *Z* configuration to afford the vinyl iodide (**27**). Palladium-catalyzed carbonylation [13] of **27** smoothly occurred when treated with carbon monooxide and tributylamine in the presence of a catalytic $Pd(OAc)_2$ (2 mol%) and PPh_3 (8 mol%) in HMPA, furnishing the lactone (**28**). Deprotection of the Boc group followed by DIBAL reduction gave the diol (**29**), which underwent smooth intramolecular cyclodehydration (CBr_4, PPh_3) to form the (*Z*)-alkylideneindolizidine (**30**). Compound **30** was converted into the iodide (**31**) as a key synthetic intermediate in three steps involving silyl protection of the tertiary alcohol, selective deprotection of the primary TBDPS ether with difluorotrimethylsilicate (TAS-F) [14], and iodination (I_2, PPh_3).

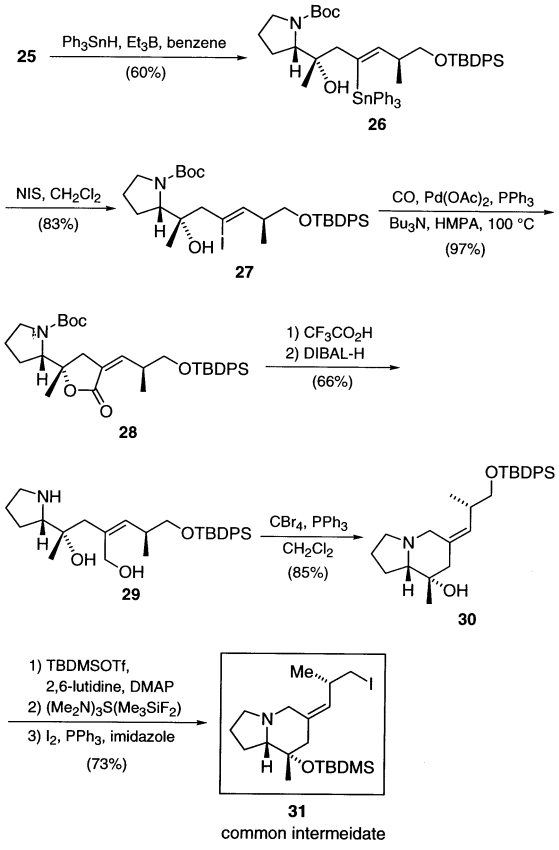
3.3. Synthesis of (+)-pumiliotoxin A via cross-coupling

We thus completed the stereoselective construction of the (*Z*)-alkylideneindolizidine (**31**) 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 (**13**) under conditions similar to those described above for the cross-coupling between **15** and **13**. The alkylideneindolizidine (**31**) was subjected to halogen–metal

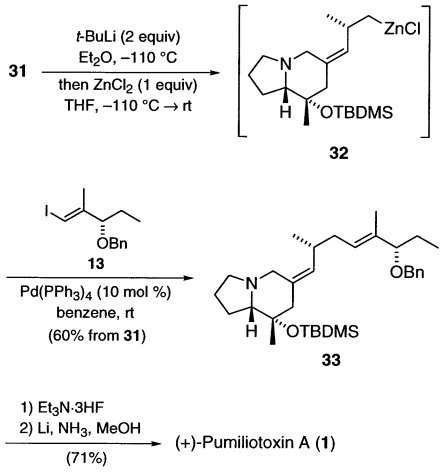


Scheme 5.

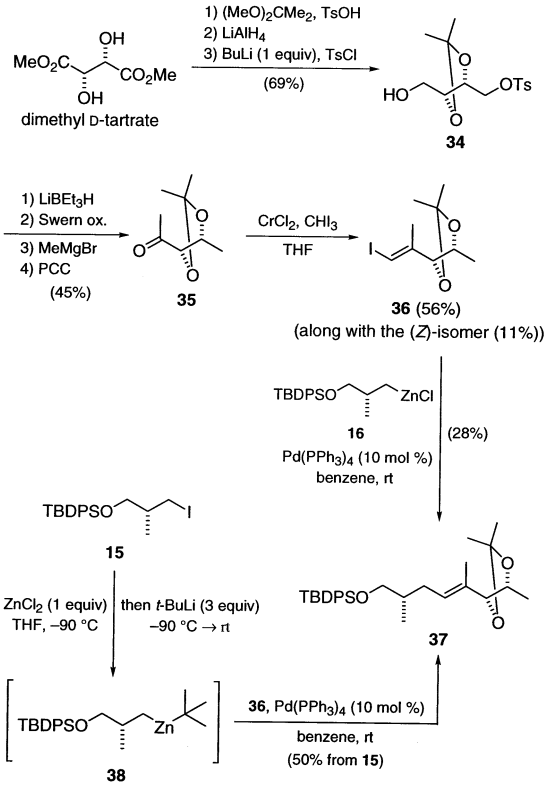
exchange (*t*-BuLi, THF, −110 °C) followed by transmetalation with $ZnCl_2$ to form the homoallylzinc derivative **32**, which underwent the cross-coupling reaction with **13** in the presence of catalytic $Pd(PPh_3)_4$ to give the cross-coupled product **33** in 60% yield from **31** (Scheme 6). Finally, removal of the TBDMS and benzyl protecting groups provided (+)-pumiliotoxin A (**1**).



Scheme 6.



Scheme 7.



Scheme 8.

4. Total synthesis of (+)-pumiliotoxin B

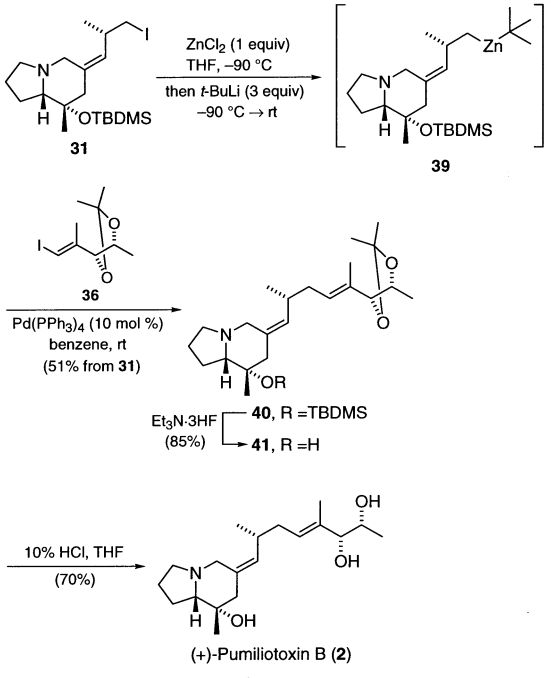
Having achieved the total synthesis of (+)-pumiliotoxin A (**1**) based on the cross-coupling reaction of the homoallylic organozinc (**32**), we next directed our efforts toward the synthesis of (+)-pumiliotoxin B (**2**) by applying the related convergent cross-coupling approach. In this case, the (*E*)-vinyl iodide (**36**) was needed for coupling with the (*Z*)-alkylideneindolizidine fragment **31**. Thus, starting from dimethyl D-tartrate, the ketone (**35**) was prepared through the alcohol (**34**) by the standard method as outlined in Scheme 8. Compound **35** was transformed via iodo-olefination using the Takai protocol ($CrCl_2$, CHI_3) [9] into the (*E*)-vinyl iodide (**36**) along with the (*Z*)-isomer in a 5.1:1 ratio. To test the possibility of exploiting **36** for the organozinc-based cross-coupling reaction, the alkylzinc reagent (**16**) described above was allowed to react with the vinyl iodide (**36**) in the presence of catalytic $Pd(PPh_3)_4$ in a manner similar to that described above for the coupling reaction of the vinyl iodide (**13**) with the alkylzinc (**16**). However, this procedure resulted in the formation of the desired cross-coupled product **37** in low yield (28%) together with a complex mixture, presumably due to accompanying cleavage of the isopropylidene acetal group caused by in situ generated Lewis acidic zinc halide.

The recent report by Smith et al. [15] demonstrated in the natural product synthesis the efficiency of a dialkylzinc derivative for the alkyl–vinyl coupling based on the modified Negishi cross-coupling reaction. In view of this protocol, we considered employing the dialkylzinc instead of the alkylzinc chloride for the cross-coupling reaction of the vinyl iodide (**36**). Hence, the dialkylzinc (**38**) was prepared by addition of one equivalent of zinc chloride to a solution of the iodide (**15**) at −90 °C followed by addition of three equivalent of *t*-BuLi. The vinyl iodide (**35**) was added to the resulting mixture along with the palladium catalyst, affording the cross-coupled product **37** in 50% yield (Scheme 7).

With these results, we were poised to incorporate the coupling reaction utilizing the dialkylzinc for the synthesis of pumiliotoxin B (**2**). Accordingly, we subjected the homoallyl iodide (**31**) to the same conditions (one equivalent $ZnCl_2$ then three equivalent *t*-BuLi) used in the preparation of the dialkylzinc (**38**), leading to the in situ formation of the homoallyl-*tert*-butyl zinc intermediate **39**. Subsequent treatment with the vinyl iodide (**36**) in the presence of the palladium(0) catalyst resulted in the homoallyl–vinyl coupling product **40**, which was deprotected using triethylamine trihydrofluoride and then HCl to provide (+)-pumiliotoxin B (**2**) (Scheme 9).

5. Conclusion

The new strategy developed herein has served to demonstrate the potential of the homoallyl–vinyl 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 novel, complex homoallylzinc molecules derived from the (Z)-iodoalkylideneindolizidine which served as an advanced common synthetic intermediate, leading to an efficient approach to the asymmetric synthesis of (+)-pumiliotoxins A and B.



Scheme 9.

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