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ABSTRACT

The asymmetric synthesis of 8-deoxypumiliotoxin **193H** and 9-deoxyhomopumiliotoxin **207O** has been achieved, starting from both enantiomers of (+)- and (−)-**10**. Enantiomerically pure alcohols (+)- and (−)-**10** were obtained by lipase-mediated kinetic resolution of racemic **10**, which was prepared in 3 steps from new lactam-type building block (−)-**8** in a highly stereoselective manner.

Introduction

To date, over 800 lipophilic alkaloids representing >20 structural classes have been detected from the skin extracts of poison frogs [1]. Pumiliotoxins (PTXs, **1**) are one of the major classes of frog alkaloids, and their structural diversity and pharmacological activity have stimulated considerable interest in their chemical synthesis by several groups. At present, over 30 alkaloids are considered to be PTXs and over 60 alkaloids belong to various congeners, such as homopumiliotoxins (hPTXs, **2**), 8-deoxy-pumiliotoxins (8-deoxy-PTXs, **3**), 9-deoxy-homopumiliotoxins (9-deoxy-hPTXs, **4**), 8-desmethyl-pumiliotoxins (8-desmethyl-PTXs, **5**), and 9-desmethyl-homopumiliotoxins (9-desmethyl-hPTXs, **6**) (Fig. 1).

Some of the proposed structures for PTXs are tentative, while others have been rigorously established by MS, FT-IR, NMR spectra, and/or synthesis. Among PTXs, over 10 enantioselective syntheses of PTX **251D** have been reported [2]; however, only one synthesis of 8-deoxy-PTX **193H** has been reported to date [3].

As part of a larger research program directed at studying the synthesis of poison frog alkaloids [4], we report here the asymmetric synthesis of 8-deoxy-PTX **193H** and 9-deoxy-hPTX **207O** (Fig. 2).

Results and discussion

The synthesis began with β-keto ester (±)-**7**, which was prepared in 3 steps from allylamine [5]. Reduction of (±)-**7** with $NaBH_4$ gave to the racemic alcohol (±)-**8** in low yield, while bakers' yeast reduction of (±)-**7** under nonfermenting conditions gave rise to the enantiopure alcohol (−)-**8** in good yield and high optical purity (>98% ee) [6]. Treatment of (−)-**8** with bis(2-methoxyethyl) azodicarboxylate and Ph_3P provided the enaminoester (±)-**9**, which was subjected to copper-mediated 1,4-addition of methyllithium, followed by reduction of the resulting adduct with Super-Hydride to afford the primary alcohol (±)-**10** in high yield as a single isomer (Scheme 1).

To obtain both enantiomers of (+)- and (−)-**10**, lipase-mediated kinetic resolution of (±)-**10** with lipase PL and vinyl acetate in *t*-BuOMe was conducted, and resulted in the acetate **11** in 55% yield with 58% ee, and the alcohol (−)-**10** in 36% yield with >98% ee, respectively. Since the ee of the acetate **11** from the initial resolution was not sufficient for further transformation, the acetate **11**

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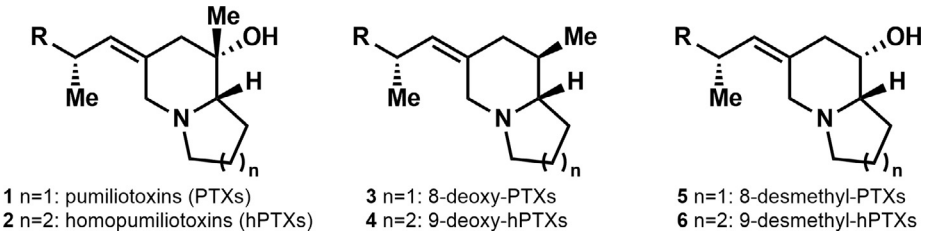


Fig. 1. Structures of pumiliotoxins and various congeners.

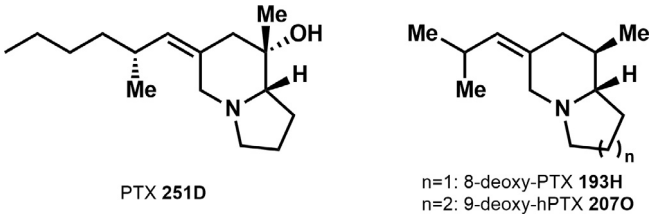
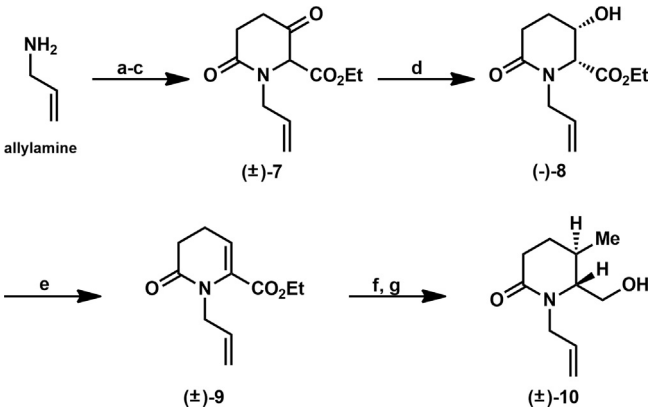
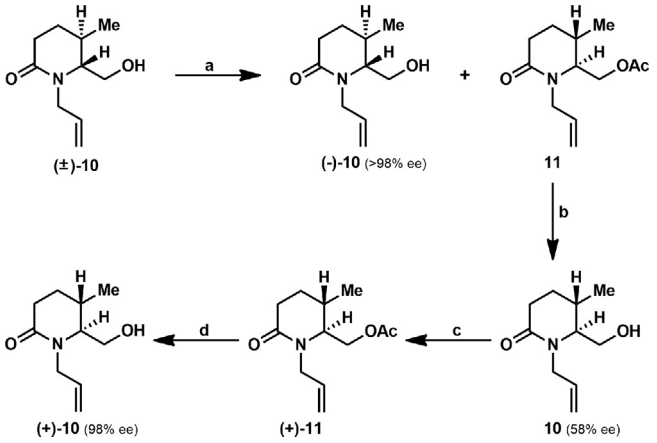


Fig. 2. Structures of PTX **251D**, 8-deoxy-PTX **193H**, and 9-deoxy-hPTX **207O**.



Scheme 1. Reagents and conditions: (a) 1.05 eq. Ethyl bromoacetate, 1.05 eq. Et_3N, CH_2Cl_2, r.t.; (b) 1.2 eq. Ethyl succinyl chloride, 1.2 eq. Et_3N, CH_2Cl_2, r.t.; (c) 1.1 eq. NaH, THF, r.t. (70% in 3 steps); (d) bakers' yeast, tap water, r.t. (76%, >98% ee); (e) 1.1 eq. bis(2-methoxyethyl) azodicarboxylate, 1.1 eq. Ph_3P, r.t. (94%); (f) 2.5 eq. Me_2CuLi, Et_2O, −78 to 0 °C; (g) 3.0 eq. Super-Hydride, THF, r.t. (92% in 2 steps).



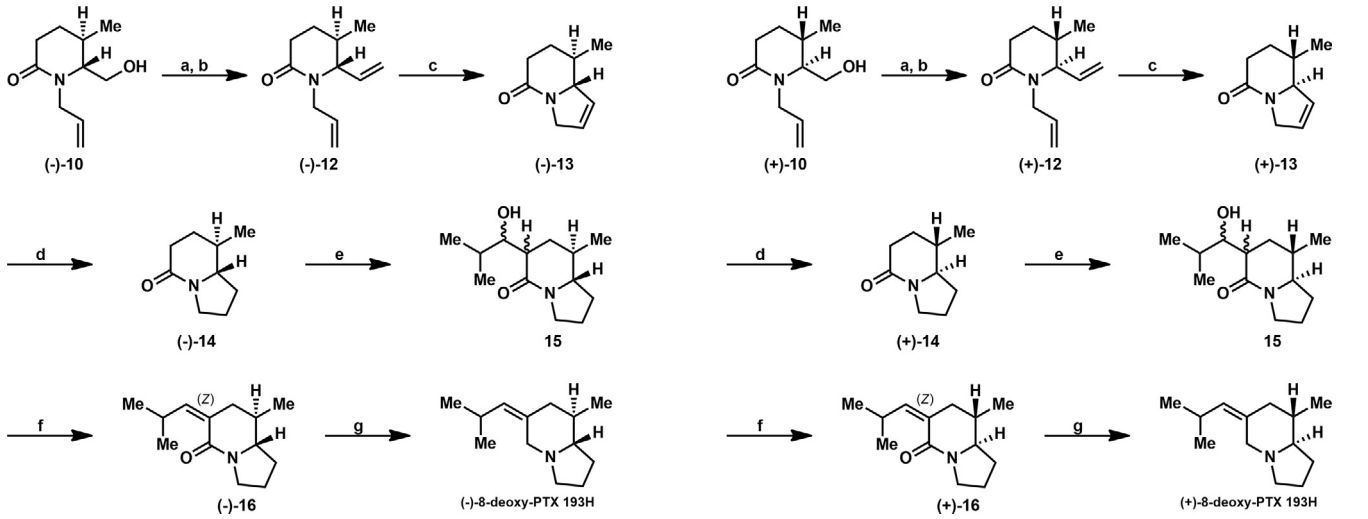
Scheme 2. Reagents and conditions: (a) lipase PL, vinyl acetate, *t*-BuOMe, r.t. ((+)-**11**: 55%, 58% ee, (−)-**10**: 36%, >98% ee); (b) 6 M NaOH (aq.), EtOH, r.t. (84%); (c) lipase PL, vinyl acetate, *t*-BuOMe, r.t. (47%); (d) 6 M NaOH (aq.), EtOH, r.t. (93%, 98% ee).

was hydrolyzed to the corresponding alcohol **10**, which was then subjected to a second kinetic resolution under the same reaction conditions to obtain the acetate (+)-**11**. Hydrolysis of the enantiopure acetate (+)-**11** with NaOH gave the enantiopure alcohol (+)-**10** with 98% ee (Scheme 2).

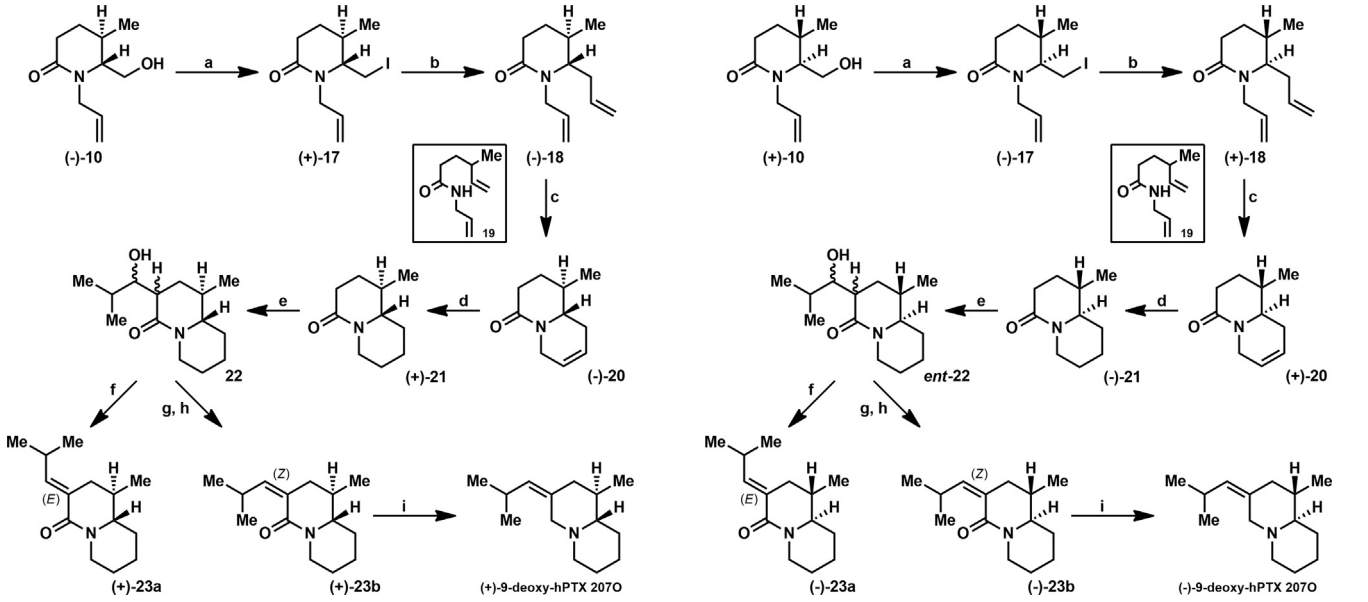
Once both enantiomers of **10** were obtained, we performed a Swern oxidation of (−)-**10**, which was followed by a Wittig reaction of the resulting aldehyde. The Wittig reaction provided the olefin (−)-**12**, which was converted to the tetrahydroindolizin-5-one (−)-**13** by ring-closing metathesis using a 2nd generation Grubbs catalyst. Hydrogenation of (-)-**13** over 10% Pd/C resulted in the indolizidinone (−)-**14**. The absolute stereochemistry of (−)-**10** was determined to be 5*R*, 6*R* by comparing the optical rotation between our synthetic (−)-**14** with known (+)-**14** [7]. Indolizidinone (−)-**14** was subjected to an aldol condensation with isobutyraldehyde to afford the aldol adduct **15**. Stereospecific *syn*-elimination of **15** using DCC/CuCl [2b] afforded the desired (*Z*)-olefin (−)-**16** with no (*E*)- olefin. Finally, a reduction of the lactam moiety of (−)-**16** using AlH_3, resulted in the formation of (−)-8-deoxy-PTX **193H** (Scheme 3). The ^1H and ^{13}C NMR spectra of our synthetic (−)-8-deoxy-PTX **193H** were in good accordance with data from the literature, however the optical rotation was opposite [3].

The enantiomer (+)-8-deoxy-PTX **193H** was also synthesized from (+)-**10** in the same manner as shown in Scheme 3.

Furthermore, both enantiomers of (+)- and (−)-9-deoxy-hPTX **207O** were also synthesized from the alcohols (−)- and (+)-**10**. The alcohol (−)-**10** was converted to the iodide (+)-**17**, which was subjected to a cross-coupling reaction with vinylmagnesium chloride in the presence of HMPA and $P(OEt)_3$ [8] to afford the diallylpiperidone (−)-**18** in 62% yield, together with the undesired ring-opening amide **19** in 22% yield, respectively. The ring-closing methathesis reaction of (−)-**18** using a 2nd generation Grubbs catalyst, followed by hydrogenation of the resulting olefin (-)-**20**, provided the quinolizidinone (+)-**21** [9], which was subjected to an aldol condensation to afford the aldol adduct **22**. Stereospecific *syn*-elimination of **22** using DCC/CuCl gave the undesired (*E*)-olefin (+)-**23a** in 81% yield, while anti-elimination [2b] by mesylation of **22**, followed by treatment of the resulting meslate with KOH, provided the desired (*Z*)-olefin (+)-**23b** in 70% yield in 2 steps. The double bond geometry in (+)-**23a** and (+)-**23b** was determined based on the chemical shift of the vinyl proton using ^1H NMR spectra. The vinyl proton of the (*Z*)-olefin (+)-**23b** was detected in a high magnetic field (δ 5.45 ppm), while that of the (*E*)-olefin (+)-**23a** was present in a low magnetic field (δ 6.56 ppm) due to the anisotropy of the amide-carbonyl group. These results are very similar to those of previous report [10]. It was noteworthy that the aldol adducts for indolizidinone **14** and quinolizidinone **21** were opposite. Finally, reduction of (+)-**23b** by treatment with AlH_3 resulted in the formation of (+)-deoxy-hPTX **207O** (Scheme 4). The enantiomer (−)-deoxy-hPTX **207O** was also synthesized from (+)-**10** in the same manner as shown in Scheme 4.



Scheme 3. Reagents and conditions: (a) 2.0 eq. $(COCl)_2$, 4.0 eq. DMSO, 6.0 eq. Et_3N, CH_2Cl_2, −78 to 0 °C; (b) 2.5 eq. $MeP^+Ph_3Br^-$, 2.25 eq. *n*-BuLi, THF, r.t.; (c) 5 mol% Grubbs catalyst 2nd generation, CH_2Cl_2, r.t.; (d) H_2, 10% Pd/C, EtOAc, r.t.; (e) 1.25 eq. isobutyraldehyde, 1.25 eq. lithium diisopropylamide, 1.25 eq. HMPA, THF, −78 to 0 °C; (f) 1.2 eq. DCC, 1.9 eq. CuCl, toluene, reflux; (g) 7.5 eq. $LiAlH_4$, 2.5 eq. $AlCl_3$, Et_2O, r.t.



Scheme 4. Reagents and conditions: (a) 1.5 eq. I_2, 1.5 eq. Ph_3P, 1.5 eq. imidazole, CH_2Cl_2, r.t.; (b) 3.3 eq. vinylmagnesium chloride, 1.1 eq. CuI, 2.2 eq. HMPA, 2.2 eq. $P(OEt)_3$, THF, −40 to 0 °C; (c) 5 mol% Grubbs catalyst 2nd generation, CH_2Cl_2, r.t.; (d) H_2, 10% Pd/C, EtOAc, r.t.; (e) 1.25 eq. isobutyraldehyde, 1.25 eq. lithium diisopropylamide, 1.25 eq. HMPA, THF, −78 to 0 °C; (f) 1.2 eq. DCC, 1.9 eq. CuCl, toluene, reflux; (g) 10.0 eq. MsCl, pyridine, r.t.; (h) 10.0 eq. KOH, MeOH, reflux; (i) 7.5 eq. $LiAlH_4$, 2.5 eq. $AlCl_3$, Et_2O, r.t.

Conclusion

We have achieved the asymmetric synthesis of both enantiomers of 8-deoxy-PTX **193H** and 9-deoxy-hPTX **207O** from the common enantiopure alcohol **10**. Furthermore, we are trying to synthesize 8-desmethyl-PTXs and 9-desmethyl-hPTXs from the enantiopure alcohol (−)-**8**. The antagonistic activities of both enantiomers of these PTX alkaloids against nicotinic acetylcholine receptors are now in progress.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.09.015.

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