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Recommended Citation
Okada, Takuya; Yamamoto, Taiga; Kato, Daiki; Kawasaki, Masashi; Saporito, Ralph; and Toyooka, Naoki, "Synthesis of 8-deoxypumiliotoxin 193H and 9-deoxyhomopumiliotoxin 207O" (2018). 2018 Faculty Bibliography. 73.
https://collected.jcu.edu/fac_bib_2018/73

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Synthesis of 8-deoxypumiliotoxin 193H and 9-deoxyhomopumiliotoxin 207O

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A R T I C L E   I N F O

Article history:
Received 31 July 2018
Revised 28 August 2018
Accepted 6 September 2018
Available online 8 September 2018

Keywords:
Asymmetric synthesis
Neotropical poison frog
Pumiliotoxin
8-Deoxypumiliotoxin 193H
9-Deoxyhomopumiliotoxin 207O

A B S T R A C T

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 NaBH4 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 Ph3P 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...
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 (+)-8-deoxy-PTX 193H in 81% yield, while anti-elimination [2b] by mesylation of (−)-13 afforded the quinolizidinone (+)-20, which was subjected to an 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. The double bond geometry in (+)-22 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 AlH3 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.
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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