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Application of Intramolecular Enyne Metathesis to the Synthesis of Aza[4.2.1]bicyclics: Enantiospecific Total Synthesis of (+)-Anatoxin-a

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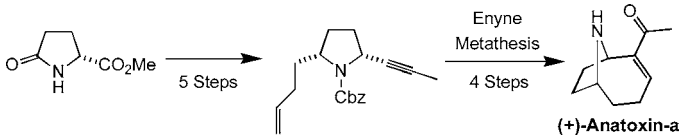
ABSTRACT



A concise synthesis of the potent nAChR agonist (+)-anatoxin-a (1) has been completed in a series of only nine chemical operations and 27% overall yield from commercially available D-methyl pyroglutamate (4). The synthesis features a novel procedure for the diastereoselective preparation of cis-2,5-disubstituted pyrrolidines leading to 10, which underwent an intramolecular enyne metathesis to afford a bridged azabicyclic intermediate that was transformed into 1.

(+)-Anatoxin-a (**1**), which was isolated from the toxic blooms of the blue-green freshwater algae *Anabaena flos-aquae* (Lyngb.) de Bréb, is one of the most potent nicotinic acetylcholine receptor (nAChR) agonists known.[1] Also referred to as "very fast death factor" (VFDF), **1** has been shown to resist enzymatic degradation by acetylcholine esterase, resulting in respiratory paralysis and eventual death.[2] Despite its toxicity, **1** has emerged as a valuable chemical probe for elucidating the mechanism of acetylcholine-mediated neurotransmission and the disease states associated with abnormalities in this important signaling pathway. Consequent to its potent pharmacological profile and unique 9-azabicyclo[4.2.1]nonane skeleton, **1** has remained an attractive synthetic target since its isolation in 1977.[3] A variety of nonlethal analogues that contain the 9-azabicyclo-[4.2.1]nonane skeleton have recently been identified as potential therapeutic targets for treating neurological disorders such as Alzheimer's and Parkinson's diseases, schizophrenia, and depression.[4]

Our interest in (+)-anatoxin-a (**1**) arose as a result of our ongoing efforts to develop ruthenium-catalyzed ring-closing

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(4) (a) Karig, G.; Large, J. M.; Sharples, C. G. V.; Sutherland, A.; Gallagher, T.; Wonnacott, S. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2825. (b) Sutherland, A.; Gallagher, T.; Sharples, C. G. V.; Wonnacott, S. *J. Org. Chem.* **2003**, *68*, 2475. (c) Gohlke, H.; Schwarz, S.; Gündisch, D.; Tilotta, M. C.; Weber, A.; Wegge, T.; Seitz, G. *J. Med. Chem.* **2003**, *46*, 2031. (d) Sharples, C. V. G.; Karig, G.; Simpson, G. L.; Spencer, J. A.; Wright, E.; Millar, N. S.; Wonnacott, S.; Gallagher, T. *J. Med. Chem.* **2002**, *45*, 3235. (e) Gohlke, H.; Gündisch, D.; Schwarz, S.; Seitz, G.; Tilotta, M. C.; Wegge, T. *J. Med. Chem.* **2002**, *45*, 1064. (f) Gündisch, D.; Kämpchen, T.; Schwarz, S.; Seitz, G.; Siegl, J.; Wegge, T. *Biorg. Med. Chem.* **2002**, *10*, 1. (g) Sharples, C. V. G.; Kaiser, S.; Soliakov, L.; Marks, M. J.; Collins, A. C.; Washburn, M.; Wright, E.; Spencer, J. A.; Gallagher, T.; Whiteaker, P.; Wonnacott, S. *J. Neurosci.* **2000**, *20*, 2783. (h) Wright, E.; Gallagher, T.; Sharples, C. V. G.; Wonnacott, S. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2867. (i) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.

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metathesis (RCM) strategies for the construction of bridged azabicycles.[5,6] In that context, we envisioned that the intramolecular enyne metathesis of the cis-2,5-disubstituted pyrrolidine **3** would generate the 9-azabicyclo[4.2.1]nonene **2** bearing a pendant alkenyl side chain that could be elaborated to the enone moiety present in **1** (Figure 1). We now report a concise enantiospecific synthesis of **1** in accordance with this strategy.

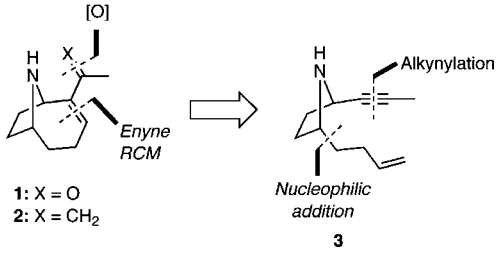
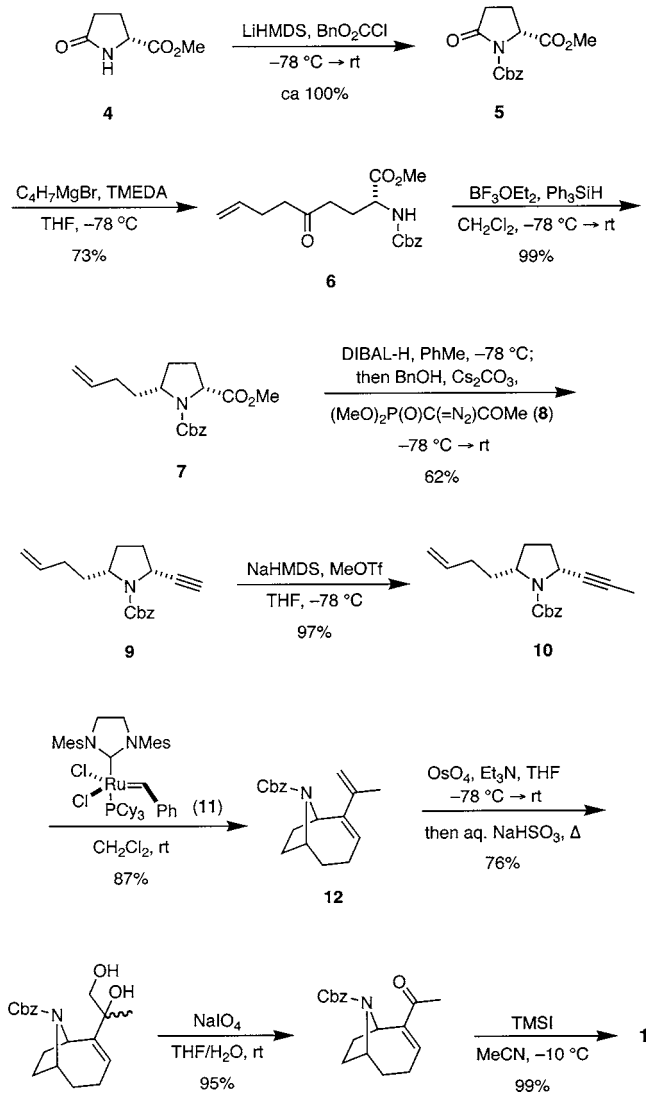


Figure 1. Retrosynthesis of (+)-anatoxin-a (**1**): key bond disconnections.

The synthesis commenced with N-protection of commercially available D-methyl pyroglutamate (**4**)[7] to provide the Cbz-lactam **5** (Scheme 1). Addition of 3-butenylmagnesium bromide to **5** in the presence of TMEDA afforded the ring-opened product **6** together with small amounts of **4**.[8] Premixing excess TMEDA and the Grignard reagent prior to reaction with **5** minimized the extent to which cleavage of the *N*-carbamoyl group occurred to form **4**.[9]

Ketone **6** was subsequently transformed into the cis-2,5-disubstituted pyrrolidine **7** (dr = 11:1)[10] by a highly diastereoselective cyclization−reduction strategy recently discovered and developed in our group.[11] In contrast to conventional hydrogenation techniques that have been employed for preparing cis-2,5-disubstituted pyrrolidines,[12] the use of triphenylsilane as the reductant allows for the incorporation of unsaturated side chains. Moreover, the bulky

Scheme 1



silane reagent provides a significant steric bias for stereoselective reduction of the transient *N*-acyl iminium ion from the less-hindered face of the pyrrolidine ring.

At this juncture, **7** was converted into the acetylene **9** exploiting a one-pot procedure that was recently reported by our group.[5a] In the event, the methyl ester moiety of **7** was reduced with DIBAL-H, and the intermediate aldehyde was treated with the diazophosphonate reagent **8** in the presence of Cs_2CO_3 to give the alkyne **9**.[13] It was necessary to perform the alkynylation step in the presence of BnOH or *i*-PrOH to prevent epimerization of the intermediate aldehyde. Alkylation of the sodium anion of **9** with MeOTf afforded the propynyl intermediate **10** in excellent yield.

The stage was thus set for the intramolecular enyne metathesis. Exposure of **10** to the Grubbs second-generation catalyst **11** at room temperature cleanly provided the 9-azabicyclo[4.2.1]nonane **12** in 87% yield. The 1,1-disub-

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(6) For additional examples of bridged azabicycles prepared by RCM, see: (a) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469. (b) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345. (c) Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255. (d) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601. (e) Pandit, U. K.; Borer, B. C.; Bieräugel, H. *Pure Appl. Chem.* **1996**, *68*, 659.

(7) Alternatively, **4** may be prepared from D-pyroglutamic acid. See: Pfaltz, A.; Leutenegger, U.; Siegmann, K.; Fritschi, H.; Keller, W.; Krathy, C. *Helv. Chim. Acta* **1988**, *71*, 1541.

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(9) In the absence of TMEDA, ketoamide **6** was obtained in only 45% yield together with substantially larger quantities of **4**.

(10) Diastereoselectivity was determined by integration of methyl ester signals in the ^{1}H NMR at 100 °C (DMSO-d_6).

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(13) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

stituted olefin in **12** was selectively dihydroxylated in the presence of the endocyclic olefin using the complex of OsO_4 and Et_3N followed by reduction of the intermediate osmate esters to afford the diol **13** along with 13% of an undesired diol that resulted from osmylation of the endocyclic alkene. The mixture of diols was readily separated by flash chromatography to afford pure **13**. Cleavage of the diol unit with periodate ion cleanly delivered **14**.[4i] Removal of the *N*-carbamoyl function was effected with TMSI at −10 °C to afford **1** in near quantitative yield. The spectral data of the synthetic **1** thus obtained were consistent with those reported in the literature.[14] To prevent light-induced decomposition of **1**,[15] the free base was converted to its hydrochloride salt with methanolic HCl at 0 °C. The hydrochloride salt of **1** also exhibited ^1H and ^{13}C NMR spectral properties consistent with those reported by Rapoport,[16] and it gave an optical rotation ($[\alpha]^{27}_D$ +37.3 (*c* 2.08, abs. EtOH)) in accord with values previously reported in the literature.[17]

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(17) Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372: $[\alpha]^{24}_D$ +36 (*c* 0.85, EtOH). See also in ref 14: $[\alpha]^{24}_D$ +43.2 (*c* 0.676, abs. EtOH).

In summary, a concise and practical synthesis of the 9-azabicyclo[4.2.1]nonane skeleton has been achieved by a strategy that features the intramolecular enyne metathesis of a cis-2,5-disubstituted pyrrolidine. The utility of this construction was demonstrated by its use in a concise enantiospecific total synthesis of (+)-anatoxin-a (**1**). The strategy is inherently flexible, thereby providing an entry to related compounds by simply modifying the nature of the side chains on the 2- and 5-positions of the pyrrolidine ring prior to metathesis. Applications of RCM reactions to the syntheses of other alkaloids constitutes the subject of a number of current investigations in our laboratories, the results of which will be reported in due course.

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Supporting Information Available: Copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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