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Synthesis of the Tetracyclic Structure of Batrachotoxin Enabled by Bridgehead Radical Coupling and Pd/Ni-Promoted Ullmann Reaction

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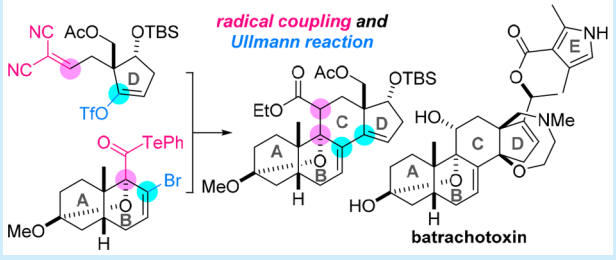
Supporting Information

ABSTRACT: The steroidal ABCD-ring system of the potent neurotoxin batrachotoxin was efficiently assembled in a convergent fashion. Bridgehead radical coupling between the simple AB-ring and D-ring fragments (**3** and **4**) formed the sterically congested linkage at the C9-oxygen-attached tetrasubstituted carbon. The C-ring was then cyclized by the Pd/Ni-promoted Ullmann reaction of the vinyl triflate and vinyl bromide of **19**, giving rise to tetracyclic structure **1**.

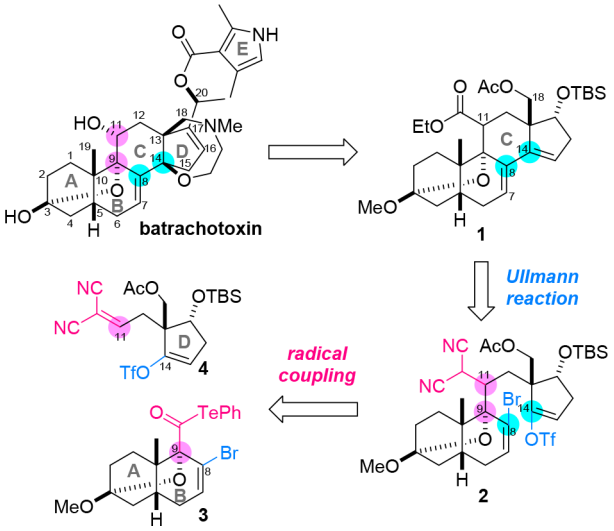


Naturally occurring steroids have a wide variety of important biological activities.[1] Therefore, many natural steroids and their synthetic derivatives are utilized as pharmaceuticals.[2] Steroidal compounds share a 6/6/6/5 ABCD-ring scaffold whose overall three-dimensional structure is controlled by the ring fusion pattern. These skeletons with distinct shapes are further varied by polar substituents and unsaturated bonds, endowing them with diverse biological functions.

Although numerous synthetic approaches to steroids have been developed,[3] highly oxygenated and unsaturated steroidal natural products continue to be a formidable synthetic challenge. This is the case because the high number of potentially reactive polar functionalities and olefins amplifies the complexity of synthetic problems. To address this issue, we have focused our efforts on designing new convergent approaches to these steroids, as such strategies are more advantageous for realizing shorter synthetic routes. We recently achieved the total syntheses of 19-hydroxysarmentogenin and ouabagenin with unusual steroidal structures by the assembly of the AB- and D-ring substructures.[4] Here we report an alternative convergent strategy for constructing the core steroidal structure of batrachotoxin (**1**, Scheme 1).

Batrachotoxin was isolated from the skins of Columbian poison-arrow frogs as a neurotoxic constituent and was structurally characterized in 1968 by Daly and Witkop.[5] Its neurotoxicity is attributed to its action to depolarize nerve and muscle membranes by selectively activating voltage-gated sodium channels.[6] Batrachotoxin belongs to the class of steroids yet possesses unique structural features such as C7- and C16-double bonds, a C9α-oxygen atom that forms the six-membered C3-hemiacetal across the AB-ring, and a C18-nitrogen atom that forms the seven-membered oxazepane ring on the CD-ring. Various creative routes to this complex architecture have been pursued,[7] culminating in the successful total syntheses of batrachotoxinin A, a C20-OH analogue, by the groups of Wehrli[8] and Kishi.[9] Most recently, the Du Bois group disclosed an efficient assembly of both enantiomers of batrachotoxin and demonstrated their agonistic activities against the channels.[10]

Scheme 1. Retrosynthesis of Batrachotoxin



Our plan for a convergent synthesis of batrachotoxin is illustrated in Scheme 1. Batrachotoxin was retrosynthetically modified to the core tetracycle **1** by removing the C14- and C17-substituents and interconverting the C11-hydroxy and C18-amino groups to the C11-ethoxycarbonyl and C18-acetoxy groups, respectively. The ABCD-ring system **1** was further disassembled into AB-ring **3** and D-ring **4**. In a synthetic direction, **3** and **4** were planned to be assembled back into **1** using two orthogonal transformations, radical coupling[11] and a transition-metal-promoted Ullmann reaction.[12] First, a C9-

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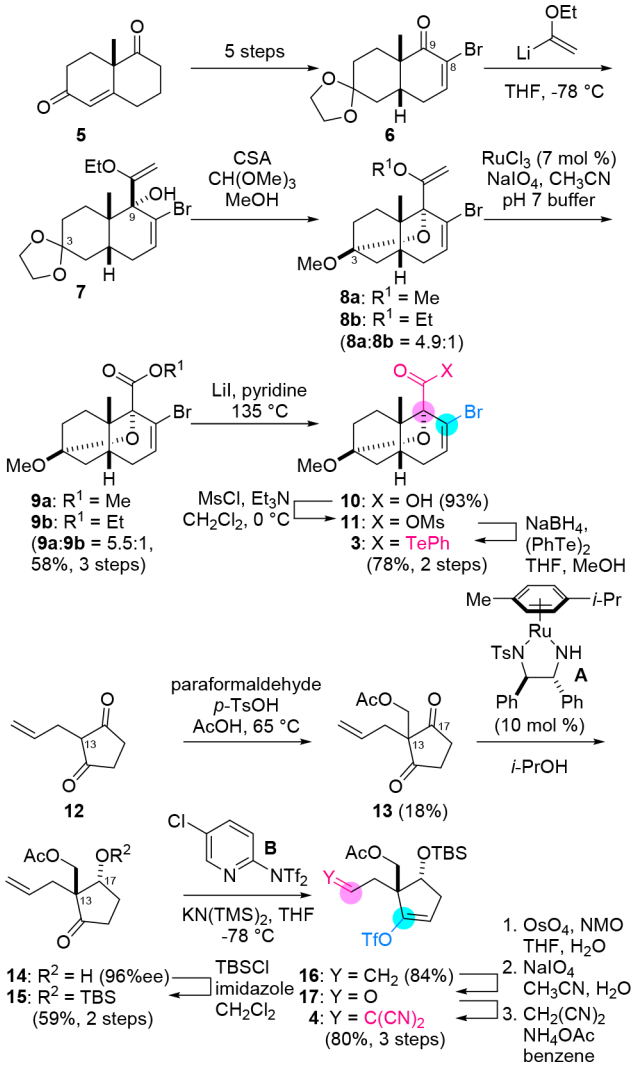
bridgehead radical,[13,14] formed from the α-alkoxy acyltelluride moiety of **3**, would be added to the electron-deficient C11-olefin of **4** to yield **2** by linking the two fragments in a C9-stereospecific manner. Second, reductive cross-coupling of the two electrophiles at the C8 and C14 positions would cyclize the C-ring to generate the steroidal skeleton of **1**. Although we recently demonstrated facile decarbonylative α-alkoxy radical formation from α-alkoxy acyltellurides,[15] radical coupling between **3** and **4** would be particularly challenging because of the presence of the highly reactive C8-vinyl bromide and C14-vinyl triflate. Nonetheless, this convergent route was expected to rapidly build up the highly oxygenated and unsaturated structure of **1** because **3** and **4** are fully equipped with all of the functional groups required for C-ring annulation.

AB-ring **3** was prepared from enantiopure Wieland–Miescher ketone **5** (Scheme 2). The five-step sequence

Scheme 2. Synthesis of the AB- and D-Ring Fragments

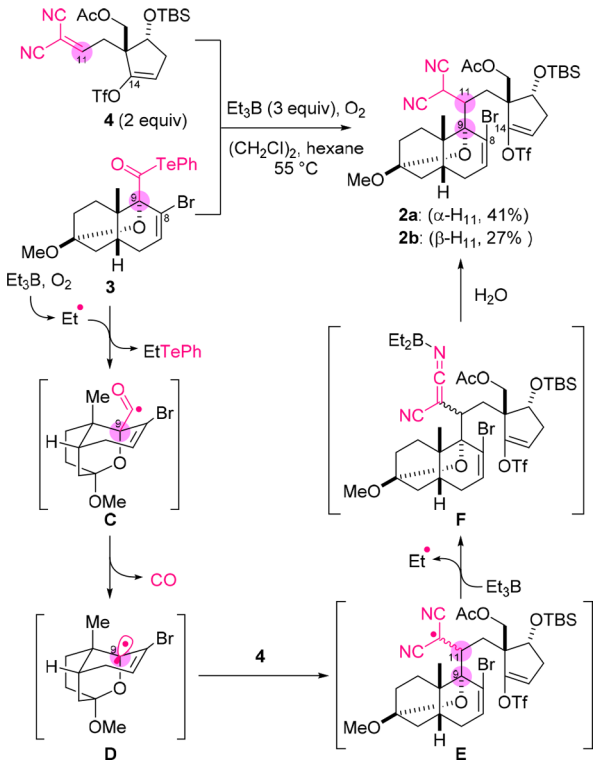


converted **5**[16] into the known C8-vinyl bromide **6**.[7g] Nucleophilic attack of lithium ethyl vinyl ether on the C9-ketone of **6** proceeded from the convex face of the *cis*-decalin system to afford **7** as the single isomer. Treatment of **7** with camphorsulfonic acid (CSA) in $CH(OMe)_3$ and MeOH induced exchange of the 1,3-dioxolane with the six-membered C3-methyl acetal and concomitantly substituted the ethyl vinyl ether with the methyl vinyl ether, leading to **8a** and **8b** (4.9:1). The **8a**/**8b** mixture was subjected to catalytic $RuCl_3$ in the presence of $NaIO_4$ to provide the ester mixture **9a**/**9b**,[17] which was treated with LiI in refluxing pyridine to generate carboxylic acid **10**.[18] Compound **10** was in turn derivatized into acyl telluride **3** in two steps: formation of the mesyl ester with MsCl and Et_3N[19] and replacement of the OMs group with the TePh group by the action of $NaBH_4$ and $(TePh)_2$.

D-ring **4** was synthesized from readily available achiral diketone **12**.[20] Treatment of **12** with *p*-TsOH and paraformaldehyde in AcOH installed the acetyl-protected hydroxy methyl group at the C13-quaternary center, leading to **13**.[21] The cyclopentadione structure of **13** was then desymmetrized by asymmetric monoreduction of diketone **13**. Namely, Ru-catalyzed asymmetric transfer hydrogenation using Noyori catalyst **A** in *i*-PrOH converted **13** to **14** with high diastereoselectivity (dr at C13 = 4:1) and excellent enantioselectivity (96% ee).[22,23] TBS protection of secondary alcohol **14** and its C13-epimer, followed by SiO_2 purification, provided enantio- and diastereopure **15**. The remaining ketone of **15** was in turn enolized with $KN(TMS)_2$ and subsequently reacted with Comins' reagent **B**[24] to furnish vinyl triflate **16**. After chemoselective oxidative cleavage of the terminal olefin of diene **16** by stepwise use of OsO_4/*N*-methylmorpholine *N*-oxide (NMO) and $NaIO_4$, the resulting aldehyde **17** was treated with malononitrile and NH_4OAc to produce the requisite D-ring **4**.

The thus-obtained AB-ring **3** and D-ring **4** were subjected to a radical coupling reaction (Scheme 3). Specifically, treatment of **3** and **4** (2 equiv) with Et_3B (3 equiv)[25] and O_2 at 55 °C resulted in the C9-stereospecific generation of a mixture of C11-diastereomers **2a** (α-C11–H, 41% yield) and **2b** (β-C11–H, 27% yield). Intermolecular formation of the sterically

Scheme 3. Bridgehead Radical Coupling of the AB- and D-Ring Fragments and Its Proposed Mechanism



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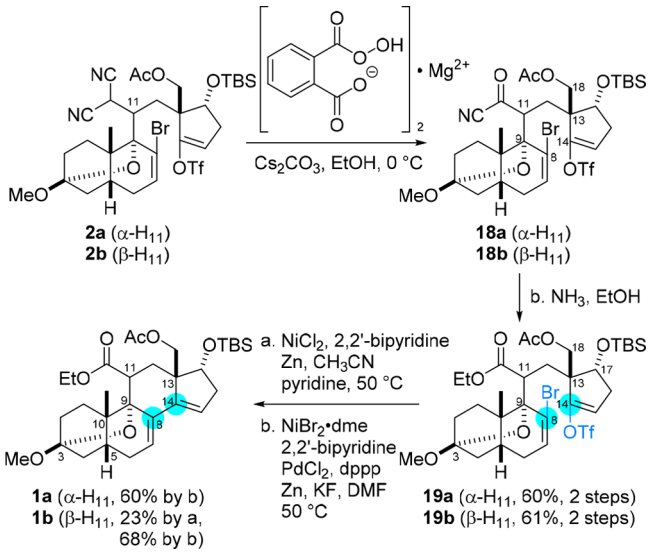
encumbered bond between tetrasubstituted C9 and trisubstituted C11 and tolerance of the C8-vinyl bromide and C14-vinyl triflate attested to the potent reactivity and high generality of the present reaction.

In this coupling, the ethyl radical generated from Et_3B and O_2 chemoselectively cleaves the weak C−Te bond of AB-ring **3** in the presence of the C8−Br bond to generate acyl radical **C**.[15] Rapid decarbonylation from **C** affords the stereochemically fixed α-alkoxy bridgehead radical **D**.[26] Because of its electron-rich and nucleophilic nature, **D** adds to the most electron-deficient alkylidenemalononitrile of **4** selectively over the C8- and C14-olefins, leading to **E**. Finally, the radical reaction is terminated by the capture of **E** by Et_3B with the expulsion of an ethyl radical,[27] and hydrolysis of the resultant **F** affords the adduct **2a**/**2b**.

After the two fragments were linked, the preinstalled C8-bromide and C14-triflate were utilized as handles for the subsequent transition-metal-promoted C-ring closure (Scheme 4). Prior to the key cyclization, a two-step sequence permitted a

Scheme 4. Pd/Ni-Promoted Ullmann Reaction for Cyclization of the C Ring



change of the malononitrile moiety of **2a**/**2b** into the ethyl ester of **19a**/**19b**. Thus, oxidation of **2a**/**2b** with magnesium monoperoxyphthalate (MMPP)[28] gave rise to acyl cyanides **18a** and **18b**, which were submitted to mild basic ethanolysis with NH_3 to yield **19a** and **19b**, respectively, without affecting the C18-OAc group.

The C-ring cyclization necessitated a powerful C−C bond formation because the reacting C8 and C14 positions were hindered by the adjacent fully substituted carbons C9 and C13. To achieve this, the Ni-promoted Ullmann reaction was first explored using one C11-isomer, **19b**. Treatment of **19b** with $NiCl_2$ (5 equiv), 2,2′-bipyridine (6 equiv), and Zn (7.5 equiv) in CH_3CN and pyridine permitted the formation of cyclized diene **1b**, albeit in only 23% yield.[29] Isolation of the C8-debrominated derivative of **19b** as a byproduct indicated the slow oxidative addition of Ni(0) to the C14−OTf bond. During this time, we noticed that the Weix group realized Ullmann cross-coupling reactions between aryl bromides and triflates by employing multimetallic Pd/Ni catalysts,[30] and we therefore expected that use of a Pd reagent would accelerate the activation of the vinyl triflate of our substrate **19b**. Although direct application of the Weix catalytic conditions was low-yielding, the stoichiometric version of the reagent system tripled the cyclization yield. When **19b** was heated to 50 °C in DMF with $PdCl_2$ (3 equiv), $NiBr_2$·1,2-dimethoxyethane (dme) (3 equiv), 2,2′-bipyridine, and 1,3-bis(diphenylphosphino)-propane (dppp) in the presence of Zn (10 equiv) and KF, the cyclized product **1b** was obtained in 68% yield. The same reaction conditions successfully transformed C11-epimeric **19a** to **1a** in 60% yield. Significantly, the acid-sensitive (C3-acetal and C17-OTBS) and base-sensitive (C18-OAc and C11-COOEt) functionalities remained intact, demonstrating the high applicability of the Pd/Ni-promoted reaction.

In summary, we have devised a new convergent strategy for constructing the steroidal framework **1a**/**1b** of batrachotoxin (15 total steps from **5**). The AB-ring **3** and D-ring **4** were designed to possess both radical and transition-metal reacting functionalities and were transformed into **1a**/**1b** in only four steps. First, a Et_3B/O_2-mediated intermolecular radical reaction between **3** and **4** was performed to form the adduct **2a**/**2b** via C9-α-alkoxy bridgehead radical **D** in a C9-stereospecific manner. Second, an intramolecular Pd/Ni-promoted reaction cyclized the six-membered C-ring by linking the congested C8−C14 bond. Noteworthily, the synthesis strategically exploited the orthogonal nature of the radical and transition-metal reactions for assembly of the highly oxygenated and unsaturated structure. Further exploration of this newly developed strategy for the total synthesis of batrachotoxin and other related steroidal natural products is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03482.

Experimental procedures, characterization data, and NMR spectra of all newly synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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