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Communication

Total Synthesis of (−)-Batrachotoxinin A: A Local-Desymmetrization Approach

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Cite This: J. Am. Chem. Soc. 2020, 142, 3675−3679
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ABSTRACT: An enantioselective total synthesis of (−)-batrachotoxinin A is accomplished based on a key photoredox coupling reaction and the subsequent local-desymmetrization operation. After the expedient assembly of the highly oxidized steroid skeleton, a delicate sequence of redox manipulations was carried out to deliver a late-stage intermediate on gram scale—and ultimately (−)-batrachotoxinin A in an efficient manner.

(−)-Batrachotoxin (Figure 1, **1**), a steroidal alkaloid with a high oxidation level, is one of the most toxic materials known to mankind.[1] First identified from the skin of *Phyllobates* poison-dart frogs in South America,[2] **1** has been widely used as an important tool for studying ion transport because it specifically stabilizes voltage-gated sodium (Na_V) channels in an active, open form.[3] Isolated together with **1**, (−)-batrachotoxinin A (**2**) is significantly less potent,[1] but it could be readily converted to **1** or other batrachotoxin analogs that serve different purposes for investigating Na_V's.[2,4] The complex structure and the uniqueness of **1** as a Na_V's agonist have made this family of natural products attractive synthetic targets for organic synthesis. As early as 1972, Imhof et al. reported a semi-synthesis of **2** starting from 11α-acetoxyprogesterone.[5] The first total synthesis of **2** was achieved by Kishi's group in a racemic manner,[6] whereas Du Bois and co-workers accomplished a 24-step synthesis of (−)-batrachotoxin (**1**) by employing an elegant radical cascade reaction.[7] In addition, Du Bois's group has revealed that analogs of (−)-batrachotoxin (**1**), including structural truncations, would be useful tools to interrogate the dynamic nature of Na_V's.[7,8] Other creative synthetic efforts have also been oriented toward this steroid skeleton, but further total synthesis studies were thwarted by the complicated ring system, contiguous stereogenic centers, and the challenging oxidation level.[9]

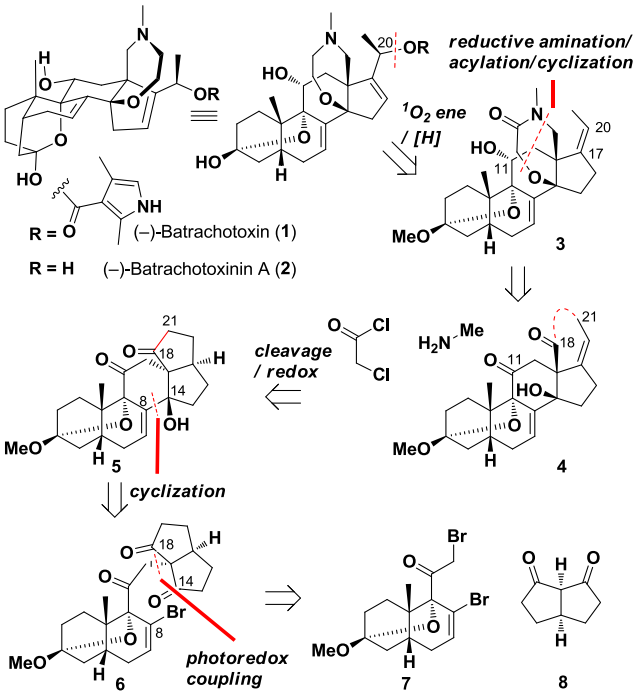


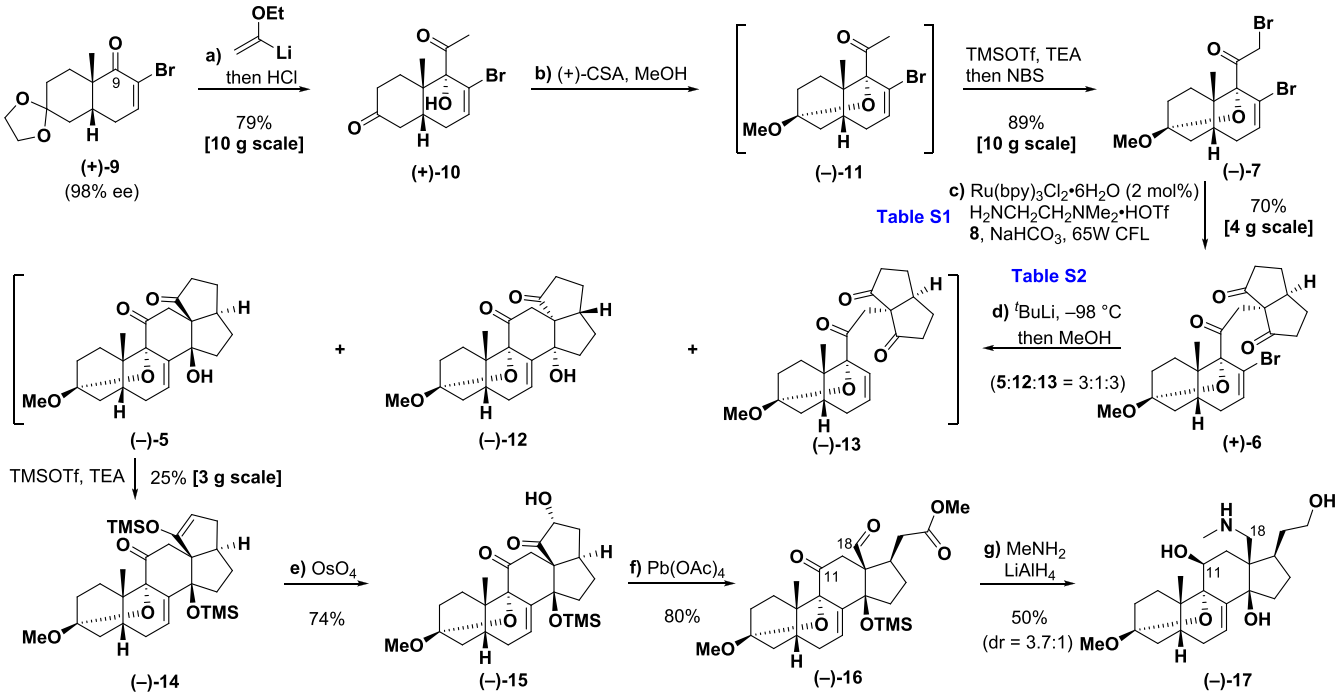
Figure 1. (−)-Batrachotoxin (**1**), (−)-batrachotoxinin A (**2**), and their retrosynthetic analyses.

The supply problem of batrachotoxin (**1**) due to the restricted natural sources,[10] together with our continued interests in highly oxidized steroids,[11] motivated us to develop a new and efficient route to (−)-**2**. We envisaged that the C20 hydroxyl group of **2** (batrachotoxin numbering, throughout) could be introduced using the singlet oxygen ene reaction of C17−C20 alkene in **3**. The seven-membered lactam ring would be traced back to aldehyde **4** by the well-established reductive amination/acylation/cyclization sequence,[5,7] while the C11 hydroxyl group might be constructed concomitantly during the reduction process. By connecting C18 and C21, we recognized a hidden symmetry of **4** that allowed us to propose a key synthetic intermediate, **5** (a shorter non-desymmetrization strategy was also attempted without success and is detailed in the Supporting Information (SI); see Scheme S1), which could be obtained from **6** by engaging the bromide to internally differentiate the two carbonyl groups (C14 and C18). This local-desymmetrization strategy significantly simplified the target structure,[12] and the precursor **6** would result from the coupling of bromide **7** and a known diketone, **8**.[13] Unlike previous tactics that generally involved a step-by-

Received: November 29, 2019
Published: February 9, 2020

https://dx.doi.org/10.1021/jacs.9b12882
J. Am. Chem. Soc. 2020, 142, 3675−3679

Scheme 1. Photoredox Coupling and Local-Desymmetrization En Route to Batrachotoxinin A (2)[a]



[a]Reagents and conditions: (a) ^{t}BuLi (5.0 equiv), ethyl vinyl ether (6.0 equiv), THF, −78 °C, 1 h; then HCl, H_2O, 1 h, rt, 79%; (b) (+)-CSA (0.1 equiv), MeOH, rt, 30 min; then TMSOTf (2.0 equiv), TEA (5.0 equiv), DCM, rt, 30 min; then NBS (1.2 equiv), $NaHCO_3$ (2.0 equiv), THF, rt, 2 h, 89%; (c) $Ru(bpy)_3Cl_2·6H_2O$ (0.02 equiv), $H_2NCH_2CH_2NMe_2·HOTf$ (1.0 equiv), **8** (4.0 equiv), $NaHCO_3$ (1.0 equiv), 65 W CFL, MeCN, rt, 3 days, 70%; (d) ^{t}BuLi (4.0 equiv), THF, −98 °C, 20 min; then MeOH (4.0 equiv); then TMSOTf (10 equiv), TEA (15 equiv), 0 °C, 20 min; then TMSOTf (4.0 equiv), TEA (10 equiv), rt, 30 min, 25%; (e) OsO_4 (1.1 equiv), THF, 0 °C, 4 h, 74%; (f) $Pb(OAc)_4$ (4.0 equiv), MeOH:DCM (1:1), 0 °C to rt, 80%; (g) $MeNH_2$ (50 equiv), DCM, 30 °C, 12 h; then $LiAlH_4$ (5.0 equiv), THF, 0 °C to reflux, 6 h, 50%. (+)-CSA, (+)-10-camphorsulfonic acid; TEA, triethylamine; NBS, *N*-bromosuccinimide.

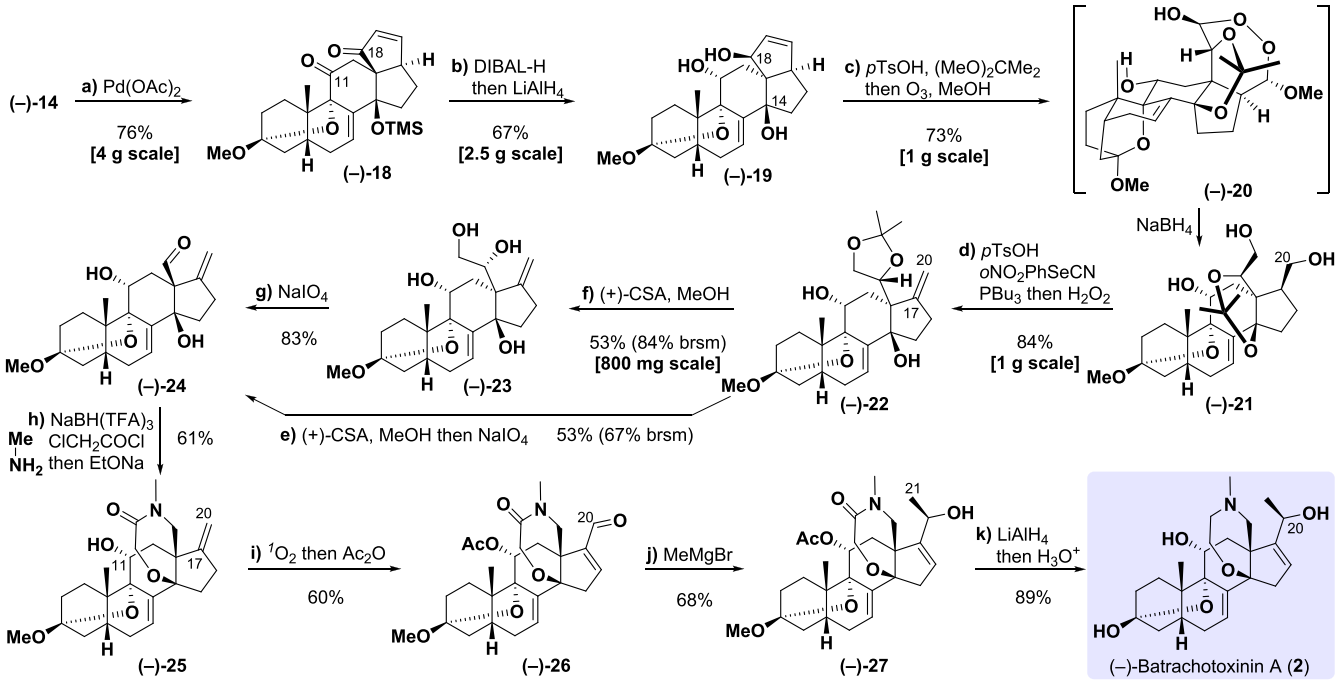
step increase of the oxidation level on the steroidal framework, our approach would access a highly oxygenated intermediate with all the "pre-built" oxidation states except C20 by enlisting the recent development of photoredox chemistry.[14] Herein, we report the materialization of this concept that led to a scalable synthesis of (−)-batrachotoxinin A (**2**).

In the forward direction, our work commenced with the preparation of enantiopure **7** and evaluation of the key coupling step (Scheme 1). Starting from (+)-**9** with excellent enantiomeric purity, prepared from (+)-Hajos−Parrish ketone in three steps,[7] we first used lithium ethyl vinyl ether to attack the C9-ketone to afford an intermediate,[9g] which underwent hydrolysis of both vinyl ether and ketal groups in the same flask to provide **10** as a single diastereomer. Methyl ketone **10** was then converted to **7** via ketal formation and the straightforward α-bromination.[15] We further streamlined the route to diketone **8** (see SI for details), providing abundant materials to enable the optimization of the coupling reaction. While the S_N2 reaction of **8** with α-bromoketone **7** was not successful under various conditions (see Figure S1 and discussion in SI for details), the open-shell radical substitution strategy served well in this scenario (Table S1).[14] In order to increase the conversion of **7** while minimizing the debromination product (**11**), we conducted the photoredox coupling reaction using an excess amount of **8** (4 equiv) and 1 equiv of $H_2NCH_2CH_2NMe_2·HOTf$ (for the formation of the SOMO-philic enamine ketone), which afforded coupling product **6** in 70% yield on a gram scale. After extensive screening of the metal−halide exchange conditions (Table S2), we found that the addition of 4 equiv of ^{t}BuLi into a THF solution of **6** under −98 °C provided the highest yield of **5**,[16] the structure of which was unambiguously determined by X-ray diffraction. The major side reaction was direct debromination (**13**), while the product resulting from the anion addition to the other carbonyl group (**12**) was the minor one (**5**:**12**:**13** = 3:1:3) (see Figure S2 and discussion in SI for a potential explanation of the preferred formation of **5** over **12**). In order to minimize the loss of materials due to the instability of **5** (retro-aldol fragmentation), we developed an in situ protection protocol, leading to the isolation of silyl ether **14** in 25% yield via gram-scale reactions. The stage was set for the cleavage of the extra five-membered ring, which started with the dihydroxylation of the electron-rich silyl enol ether in **14** to provide hydroxyketone **15**. To our delight, subjecting **15** to $Pb(OAc)_4$ in MeOH afforded aldehyde **16** in 80% yield, ready for the subsequent reductive amination to install the C18-amino group.[17] Formation of imine followed by treatment with excess $LiAlH_4$ led to not only global reduction but also removal of the TMS protecting group, delivering amine **17** in 50% yield with 3.7:1 diastereoselectivity on the C11 hydroxyl group. Unfortunately, the major diastereomer was the undesired one, as determined by X-ray crystallography, which would require the inversion of the C11 stereogenic center in the later stage of synthesis. Therefore, we deprioritized this approach and shifted our attention to securing the correct C11 stereogenic center in a different way.

In designing an alternative route to complete the total synthesis (Scheme 2), we envisioned that the correct C11

https://dx.doi.org/10.1021/jacs.9b12882
J. Am. Chem. Soc. 2020, 142, 3675−3679

Scheme 2. Completing the Total Synthesis of (−)-Batrachotoxinin A (2)[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$ (1.0 equiv), MeCN, rt, 2 h, 76%; (b) DIBAL-H (2.4 equiv), DCM:ether (4:1), −78 °C, 1 h; then $LiAlH_4$ (10 equiv), −78 °C, 2 h, 67%; (c) *p*TsOH·H_2O (0.1 equiv), $(MeO)_2CMe_2$:DCM (1:1), rt, 1 h; then O_3, MeOH, −78 °C, 5 min; then $NaBH_4$ (20 equiv), MeOH:H_2O (1:1), 60 °C, 20 h, 73%; (d) *p*TsOH·H_2O (0.01 equiv), $(MeO)_2CMe_2$ (0.05 equiv), DCM, 0 °C, 1 h; then *o*NO_2PhSeCN (3.0 equiv), PBu_3 (4.0 equiv), THF, rt, 46 h; then H_2O_2 (20 equiv), 0 °C to rt, 40 h, 84%; (e) (+)-CSA (0.1 equiv), MeOH:DCM (1:1), 0 to 30 °C, 18 h; then $NaIO_4$ (2.0 equiv), THF:H_2O (1:1), 0 °C, 1 h, 53% (67% brsm); (f) (+)-CSA (1.0 equiv), MeOH, 0 to 30 °C, 8 h, 53% (84% brsm); (g) $NaIO_4$ (2.0 equiv), THF:H_2O (1:1), 0 °C, 1 h, 83%; (h) $MeNH_2$ (20 equiv), DCM, 30 °C, 12 h; then $NaBH(TFA)_3$ (1.5 equiv), DCM, −78 °C, 20 min; then $ClCH_2COCl$ (2.0 equiv), 2,6-lutidine (8.0 equiv), −78 to 0 °C, 2 h; then EtONa (10 equiv), EtOH, rt, 3 h, 61%; (i) TPP (0.02 equiv), O_2 (1 atm), CCl_4, rt, 4 days; then Ac_2O (3.0 equiv), DMAP (4.0 equiv), DCM, 0 °C to rt, 15 h, 60%; (j) MeMgBr (3.0 equiv), THF, −78 °C, 30 min, 68%; (k) $LiAlH_4$ (5.0 equiv), THF, reflux, 4 h; then HCl (aq.), 1 h, rt, 89%. TPP, *meso*-tetraphenylporphin.

stereogenic center could be obtained via the hydroxyl-directed reduction. Therefore, we first converted **14** to enone **18** via Saegusa oxidation. After careful optimization, DIBAL-H reduction of the C18 carbonyl group (Figure S3), followed by treatment with $LiAlH_4$ in excess, which simultaneously achieved the removal of the TMS protecting group and C11 carbonyl reduction, successfully converted **18** to triol **19** in 67% yield. Protection of C14 and C18 hydroxyl groups with acetonide and selective ozonolysis of the disubstituted olefin in one pot furnished **20** (see SI), which was then reduced by $NaBH_4$ in situ to afford triol **21** in 73% yield. Transketalization of the acetonide protecting group to the 1,2-diol was completed upon the treatment with *p*TsOH, and Grieco−Nishizawa elimination of the C20 primary alcohol was executed in the same flask to introduce the C17−C20 alkene.[18] The resulting product, **22**, was subjected to one-pot deprotonation under acidic conditions and oxidative cleavage to furnish aldehyde **24** in 53% yield (67% based on the recovery of starting material). Considering the better stability of tetraol **23** with respect to aldehyde **24**, the synthesis on a larger scale was done in two steps, with preparation of **23** (382 mg) in 84% yield based on recovered starting material, followed by oxidation to **24** in 83% yield. Subsequently, a one-pot, three-step sequence of reductive amination, acylation, and cyclization was applied to forge the homomorpholinamide ring to access **25**, completing the full skeleton of **2**.[7] The singlet oxygen ene reaction of the C17−C20 alkene turned out to be rather sluggish; acetic anhydride treatment after 4-day irradiation afforded aldehyde **26** in 60% yield, while the product resulting from acetylation of the C11 hydroxyl group of the unreacted starting material was isolated in 19% yield, which could be further converted to **26** under the same reaction conditions (see SI). The installation of the last carbon (C21) was achieved by the nucleophilic attack of methyl Grignard reagent to the C20-aldehyde, and the major diastereomer, **27**, was isolated in 68% yield. Eventually, $LiAlH_4$ reduction followed by acid-promoted deprotection gave the target compound (−)-**2** in 89% yield. The last two steps could be carried out in a one-pot fashion to afford **2** in 61% yield with 6:1 diastereoselectivity at C20 (see SI).[19] All of the analytic data for the synthesized sample of **2** were consistent with those reported in the literature (Table S3).[5,7]

In summary, the total synthesis of (−)-batrachotoxinin A (**2**) was achieved via a route slightly different from our original plan proposed in Figure 1 (Scheme S2). Even though we were not able to further improve the efficiency of the halide-exchange/intramolecular cyclization step (Table S2), our route was successfully streamlined to be executed on gram scale until the late-stage intermediate **23**. Due to the known toxicity issues of **1** and **2** bearing the basic amine moiety, the last steps were performed on a much smaller scale. This development not only secures the supply of **1** and its analogs for basic research but also enables the deep-seated structural changes of batrachotoxin in a flexible manner. Importantly, our strategy—photoredox coupling of two fragments with high oxidation levels followed by intramolecular cyclization—could be

https://dx.doi.org/10.1021/jacs.9b12882
J. Am. Chem. Soc. 2020, 142, 3675−3679

extended to the syntheses of other highly oxidized natural products, which is under way and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12882.

Experimental procedures and spectral data for all new compounds (PDF)
X-ray crystallographic data for (±)-**5** (CIF)
X-ray crystallographic data for (+)-**6** (CIF)
X-ray crystallographic data for (−)-**7** (CIF)
X-ray crystallographic data for (±)-**12** (CIF)
X-ray crystallographic data for (±)-**14** (CIF)
X-ray crystallographic data for (−)-**15** (CIF)
X-ray crystallographic data for (−)-**17** (CIF)
X-ray crystallographic data for (±)-**20** (CIF)
X-ray crystallographic data for (+)-**S6** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by College of Chemistry and Molecular Engineering, Peking University and Peking-Tsinghua Center for Life Sciences, Beijing National Laboratory for Molecular Sciences, the National Science Foundation of China (Grant Nos. 31521004, 21672011, and 21822101), and the National Key Research and Development Program of China (Grant No. 2017YFA0104003). We thank Prof. J. Du Bois (Stanford University) for helpful discussions, and Prof. Sanzhong Luo (Tsinghua University) for help in the photoredox chemistry. The measurements of NMR, mass spectrometry, and XRD were performed at the Analytical Instrumentation Center of Peking University. We acknowledge the assistance and support from PKUAIC (Dr. Jie Su) and support from the High-Performance Computing Platform of Peking University.

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(19) One reaction step is defined as the conversion of a substrate to a product in a single reaction flask without intermediate workup or purification. See: Kawamura, S.; Chu, H.; Felding, J.; Baran, P. S. Nineteen-step total synthesis of (+)-phorbol. *Nature* **2016**, *532*, 90−93.

https://dx.doi.org/10.1021/jacs.9b12882
J. Am. Chem. Soc. 2020, 142, 3675−3679