Total Synthesis of (±)-Batrachotoxinin A

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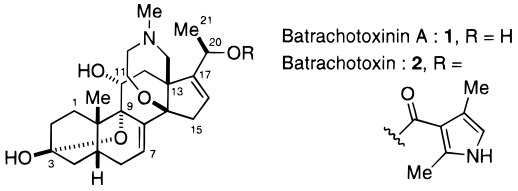
Received April 14, 1998

The batrachotoxins are a unique class of steroidal alkaloids isolated in minute quantities from the skins of poison arrow frogs (genus *Phyllobates*)[1] as well as from the feathers of a New Guinea bird (genus *Pitohui*).[2] The structures of batrachotoxinin A (**1**) and batrachotoxin (**2**) were unambiguously determined through X-ray analysis[3] and chemical correlation,[4] respectively. The

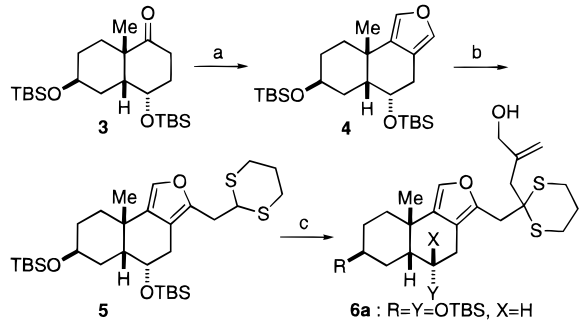


batrachotoxins exhibit a number of unique structural features, including a steroid-based pentacyclic core skeleton, an intramolecular 3β-hemiketal, and a seven-membered oxazapane ring. These compounds are extremely potent neurotoxins (batrachotoxin, LD_{50} in mice 2 μg/kg) that act as selective and irreversible Na^+-channel activators.[5]

A partial synthesis of (−)-batrachotoxinin A from (+)-progestrone was accomplished in 1972 by Imhof and co-workers,[6] while several synthetic efforts toward the ABC ring system have been recorded.[7] In this paper, we report the first total synthesis of (±)-batrachotoxinin A, which also constitutes a formal total synthesis of (±)-batrachotoxin.[4] Strategic bond-forming events include an intramolecular furan Diels−Alder reaction[8] to assemble the steroidal skeleton, an intramolecular oxy-Michael reaction[9] to close the oxazapane ring,[10] and an organocerium addition to form the C20−C21 bond.[11]

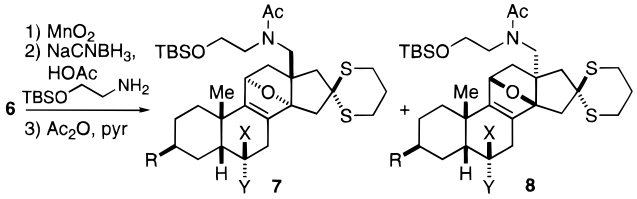
Employing the method of Garst and Spencer,[12] the (±)-cis-decalone **3**[13] was transformed into the fused-furan **4** (Scheme 1). This intermediate was elaborated in a regioselective fashion to

Scheme 1[a]



[a] Reagents and yields: (a) (i) ethyl formate, NaH; (ii) *n*-BuSH, TsOH (88%); (iii) Me_3SI, NaHMDS;[12] (iv) $HgCl_2$ (54%); (b) (i) DMF, $(COCl)_2$ (84%); (ii) KO*t*-Bu, $CH_3OCH_2P(Ph)_3Cl$; (iii) 1,3-propanedithiol, CSA (72%); (c) (i) *t*-BuLi, HMPA, 2-(bromomethyl)-1-(*tert*-butyldimethylsilyloxy)-2-propene; (ii) TBAF (52%).

Scheme 2



entry	R	X	Y	yield, %	ratio (**7**:**8**)
a	OTBS	H	OTBS	70-75	>25:1
b	OTBDPS	H	H	75-80	3-4:1
c	OTBDPS	OMPM	H	40-50	1.4:1

provide the corresponding 1,3-dithiane **5**. In two additional steps, the dithiane was alkylated and selectively deprotected to afford the Diels−Alder precursor **6**.

Using MnO_2 in dichloromethane, the allylic alcohol **6a** was cleanly oxidized to the corresponding enal, which smoothly underwent intramolecular [4 + 2] cycloaddition (Scheme 2). Without purification, the cycloadduct was directly subjected to reductive amination and then acetylation to afford a single diastereomer **7a** in 70−75% yield. Interestingly, we have discovered that the selectivity of the Diels−Alder reaction is dramatically influenced by the C6 substituent. In fact, a C6 deoxy analogue (**6b**) provided the corresponding cycloadduct in only **7b**:**8b** 3−4:1 diastereoselectivity,[14] while the C6 β-OMPM derivative **6c** underwent [4 + 2] cycloaddition in a poor (**7c**:**8c** 3:2) selectivity. The structures of **7** and **8** were determined through X-ray analysis and/or extensive NMR studies, establishing that both **7** and **8** result from endo-mode transition states in the Diels−Alder reaction.

Through NOE experiments, we have ascertained that **6a** exists in a single chair−chair conformer **A**,[15] while **6c** predominantly adopts the alternative chair−chair conformer **B** (Figure 1). In both cases, the C6 substituent occupies a favorable equatorial position. In contrast, **6b** exists as a mixture of conformers **A** and **B**. For the endo-mode [4 + 2] cycloaddition of **6a**, an α-face approach of the dienophile to the furan is effectively shielded (cf. Newman projection of conformer **A**), whereas in the endo-mode cycloaddition of **6c**, both the α- and β-face approaches are sterically accessible (cf. Newman projection of conformer **B**).

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(13) Decalone **3** was prepared from (±)-Weiland−Miescher diketone; see the Supporting Information for details.

(14) Previously, we reported that substrate **6b** undergoes an intramolecular [4 + 2] cycloaddition in the presence of Me_3Al at −78 °C to afford an 8:1 ratio of diasteromers (see ref 10a). However, these optimized conditions were not compatible with the subsequent reductive amination.

(15) The A ring of conformer **A** might be somewhat distorted with the C3 OTBS group turning away from the axial position to relieve considerable 1,3-diaxial interations, thereby providing more steric shielding of the α-face approach in the [4 + 2] cycloaddition.

S0002-7863(98)01258-X CCC: $15.00
Published on Web 06/18/1998

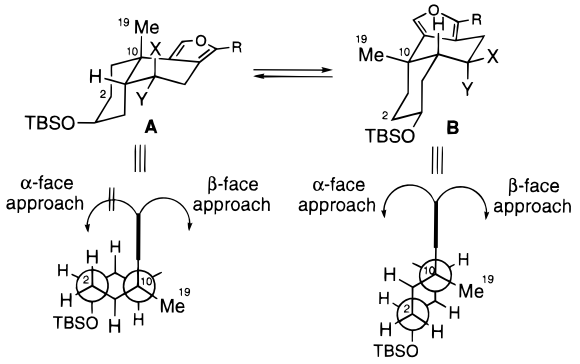
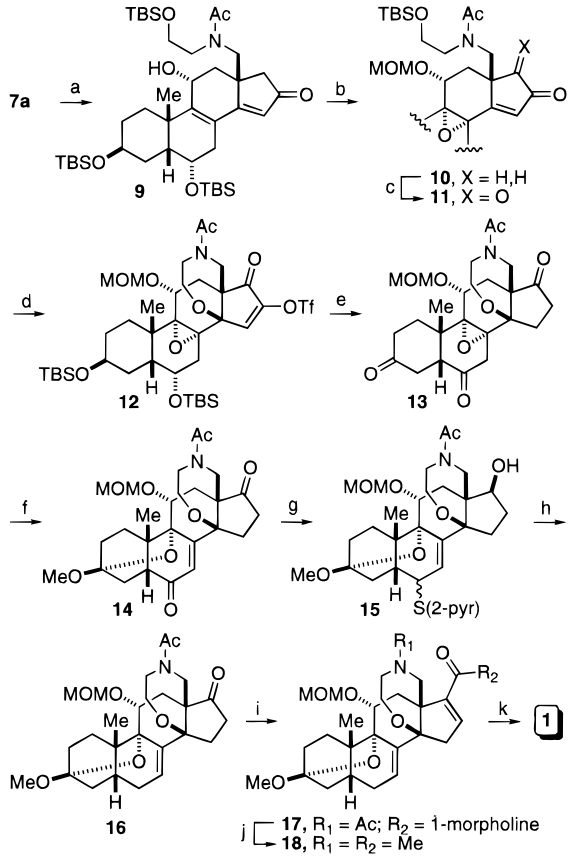


Figure 1.

Scheme 3[a]



[a] Reagents and yields: (a) (i) $(CF_3CO_2)_2IC_6H_5$,[22] $CaCO_3$, MeOH; (ii) PPTS, acetone; (iii) DBU (68%); (b) (i) *p*-nitroperoxybenzoic acid (90%); (ii) MOMCl, DIEA (93%); (c) (i) KHMDS, Davis' oxaziridine[23] (93%); (ii) TFAA, DMSO, TEA (88%); (d) (i) $(Me_2N)_3S(Me_3SiF_2)$;[17] (ii) $PhNTf_2$, TEA (95%); (e) (i) PtO_2, H_2, 2,6-di-*tert*-butylpyridine (90%);[18] (ii) $NaBH_4$; (iii) TBAF; (iv) Dess−Martin oxidant; (f) (i) DBU; (ii) CSA, MeOH (85%); (g) (i) $NaBH_4$, $CeCl_3$; (ii) 2,2′-dipyridyl disulfide, (*n*-Bu)$_3$P; (h) (i) W-2 Raney Ni, H_2; (ii) Dess−Martin oxidant[20] (73%); (i) (i) KHMDS, $PhNTf_2$; (90%); (ii) $Pd(PPh_3)_4$, CO, morpholine (96%);[21] (j) (i) $CeCl_3$, MeLi;[11] (ii) $NaHCO_3$, MeI (80%); (k) (i) $Zn(BH_4)_2$ (80%); (ii) *p*-TsOH, wet acetone (83%).

Cycloadduct **7a** was readily transformed into the corresponding dienone **9** after dithiane deprotection and base treatment (Scheme 3). Subsequently, the allylic alcohol was subjected to a hydroxyl-directed epoxidation to provide, after protection, the epoxy enone **10** in good yield. The enone **10** was then converted into the corresponding α-keto enone **11** using standard methods.

In a previous report, we had noted that incorporation of a C15 carbomethoxy ester was necessary in order to effect an oxy-Michael addition.[10b] Now, we report that the α-keto enone **11** is also a suitable substrate for this reaction.[16] Furthermore, this modified approach facilitates C17 functionalization for installation of the requisite hydroxyethyl side chain. In the event, deprotection of the primary silyl ether using TASF,[17] followed by trapping with $PhNTf_2$, afforded the desired Michael-adduct **12** in 95% yield. Hydrogenolysis of the enol triflate could be achieved using platinum oxide and hydrogen to provide,[18] after further manipulations, triketone **13** in good yield.

Originally, we had envisioned installing the C7−C8 olefin through ring-opening of a C8−C9 tetrasubstituted epoxide.[19] Unfortunately, this strategy was not successful, presumably due to considerable steric constraints on the α-face around C7−C9. Thus, we chose to slightly modify our original route to include a C6 ketone that could be used to facilitate deprotonation of the C7 position. Indeed, epoxide opening and ketal formation to provide **14** could be smoothly accomplished in two steps from **13**. Removal of the C6 ketone was then achieved through a Luche reduction, selective C6 pyridylthioether formation, Raney nickel desulfurization, and Dess−Martin oxidation.[20] The structure of intermediate **16** was secured through X-ray analysis.

The remaining challenge was incorporation of the requisite C17 hydroxyethyl side chain. Two approaches to accomplish this task could be imagined: (1) nucleophilic additions to the C17 ketone and (2) metal-catalyzed couplings of the C17 enol triflate. Considering the sterically encumbered environment of this ketone as well as the somewhat electrophilic nature of the *N*-acetyl group, we pursued the second approach. Thus, the enol triflate of ketone **16** underwent palladium-catalyzed carbonylation[21] in the presence of morpholine to afford amide **17** in 96% yield. This amide was readily converted to the desired methyl ketone, and the *N*-acetyl protecting group was simultaneously removed upon reaction with an excess of freshly prepared "$MeCeCl_2$".[11] Subsequent methylation of the secondary amine provided intermediate **18** in 80% overall yield.

After an extensive survey of reducing agents, it was discovered that the α-enone could be selectively reduced using zinc borohydride in diethyl ether to provide the desired allylic alcohol as a 5:1 mixture of diastereomers. Finally, acidic deprotection furnished (±)-batrachotoxinin A (**1**). The synthetic material was determined by ^{1}H NMR, MS, and TLC to be identical to a sample of natural **1**.[24] Since the chemical transformation of (−)-**1** into (+)-**2** is known,[4] this synthesis constitutes a formal total synthesis of (±)-batrachotoxin.

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support (NS 12108). L.R.M. also thanks the National Cancer Institute for a postdoctoral fellowship (5 F32 CA72230).

Supporting Information Available: Complete experimental details including characterization for all new compounds (19 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981258G

(16) The C17-ketone group not only activates the *β*-position of the enone but also stabilizes the enolate of the oxy-Michael adduct. Deprotection of the primary TBS group in **11** using HF·pyr gave the seven-membered hemiketal between the primary alcohol and the C17 ketone. Under basic conditions, this isolable product smoothly underwent the oxy-Michael cyclization.

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