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Formal Synthesis of (±)-Tetrodotoxin via the Oxidative Amidation of a Phenol: On the Structure of the Sato Lactone

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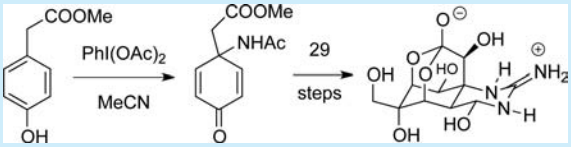
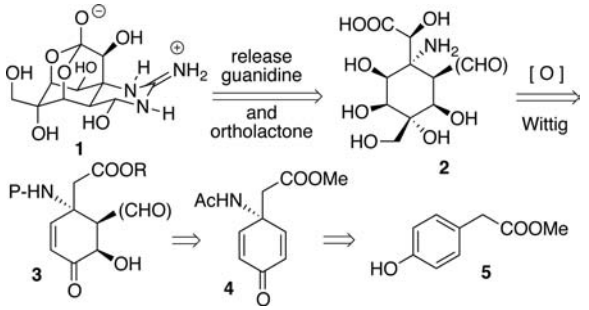
Supporting Information

ABSTRACT: A formal total synthesis of (±)-tetrodotoxin that relies on the bimolecular oxidative amidation of a phenol is described, and a structural correction of the Sato lactone, an important tetrodotoxin intermediate, is provided. This work lays the foundation for an ultimate enantioselective synthesis.



This paper describes a formal synthesis of the racemate of the potent neurotoxin, tetrodotoxin (TTX, **1**),[1−4] that relies on an early stage, bimolecular oxidative amidation of a phenol[5] as a key step. Scheme 1[6] shows that **1** could be reached

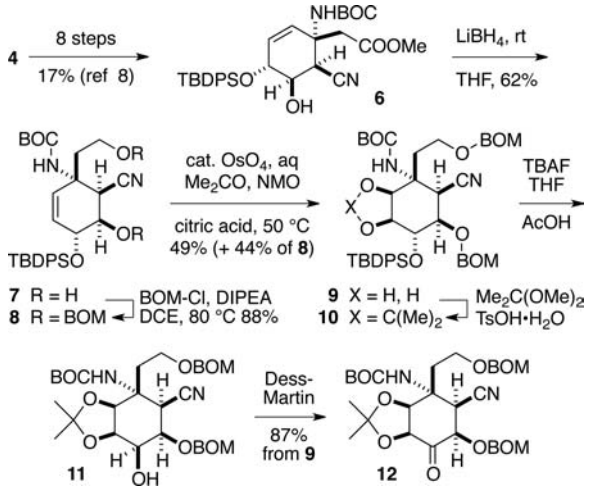
Scheme 1. Retrosynthetic Logic for Tetrodotoxin (1)



through elaboration of **4** into **3** (the parentheses signify that the CHO group may be either expressed or latent) and then into **2**. Substance **4** is a known product of oxidative amidation of phenol **5**.[7]

Compound **4** was advanced to hydroxynitrile **6** according to a recently described procedure[8] that involves a Machetti−De Sarlo[9] reaction as a crucial step (Scheme 2).[10] The processing of **6** toward TTX started with reduction of the ester and BOM protection of both OH groups. The subsequent dihydroxylation of the emerging **8** (cat. OsO_4, excess NMO, citric acid)[11] proceeded slowly, requiring 110 h at 50 °C to achieve just over 50% conversion. Diol **9** was thus obtained in 49% yield, together with 44% of unreacted **8**. On the other hand, the reaction occurred in a highly diastereoselective manner in accord with the Kishi *anti*-directing effect of the allylic silyl ether.[12] It should be noted that the stereochemical outcome of this step was by no means certain at the onset of this investigation. Indeed, Donohoe and collaborators have shown that certain allylic secondary amides exert a significant *syn*-directing effect in osmylation reactions, apparently through H-bonding.[13] In the case of **8**, the two effects would operate in opposition to each other. Although the Donohoe effect seems to pertain to reactions run in aprotic solvents (e.g., pyridine)

Scheme 2. Elaboration of Dienone 4 to Ketone 12



with stoichiometric OsO_4, the relative directing power of the allylic OTBDPS and NHBOC groups was difficult to predict in a substrate as complex as **8**. Happily, it transpired that the *syn*-directing effect of the *tert*-butyl carbamate is insignificant in the present case. Diol **9** was immediately protected as acetonide **10**, the desilylation of which, followed by Dess-Martin oxidation[14] of the resultant **11**, afforded ketone **12**.

Further elaboration of the newly prepared ketone toward (±)-tetrodotoxin required an olefination of the keto functionality and a dihydroxylation of the resultant exomethylene derivative. Whereas compound **12** proved to be a poor substrate for Wittig reaction, addition of $TMSCH_2Li$ took place smoothly to give an isolable adduct, which, however, afforded the desired alkene only upon treatment with PPTS[15] (Scheme 3). Interestingly, the target product was obtained in the form of amide **13**. The unexpected hydration of the nitrile was rationalized as follows. The addition of $TMSCH_2Li$ to **12** proceeded in a highly Felkin−Ahn[16] selective manner to give

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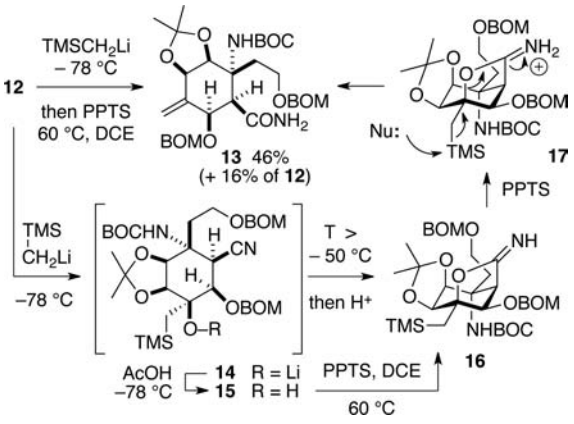
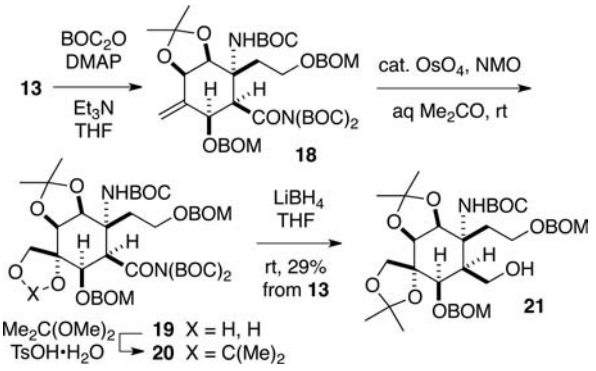
Scheme 3. Mechanism of Formation of Amide 13



14. Quenching the reaction at −78 °C (AcOH) led to the isolation of **15**, but warming the reaction mixture containing **14** above −50 °C, prior to mild acidic quenching, caused cyclization of **14** to **16**, which was also isolated. Treatment of **16** with PPTS triggered fragmentation to **13**, arguably via species **17**. Alcohol **15** also produced **13** upon exposure to PPTS, suggesting that cyclization to **16** is likely to take place prior to olefin formation.

The amide function in **13** was converted into the *N*,*N*-bis-BOC derivative **18** (Scheme 4) in preparation for an eventual

Scheme 4. Assembly of Tetrodotoxin Precursor 21



reduction to an alcohol.[17] The latter operation was best postponed until after a second, highly Kishi-selective osmylation of the exomethylene unit[18] and acetonide formation. Reduction[17] of **20** delivered alcohol **21**,[19] thus obtained in 20 steps from **5**.

At this point, safety considerations dissuaded us from advancing **21** to highly hazardous **1**. A strategic decision was made to convert it into lactone **22** (Figure 1), recognized as the Sato tetrodotoxin precursor.[3f–h] This would constitute a formal synthesis of (±)-**1**.

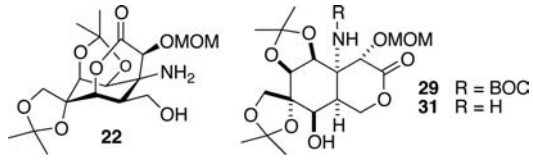
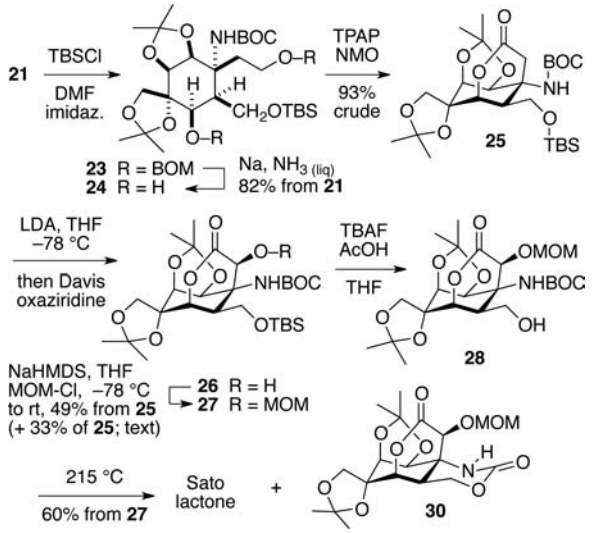


Figure 1. Structures of presumed Sato lactone, **22**, byproduct **29**, and actual Sato lactone, **31**.

The route to **22** (Scheme 5) started with TBS protection of **21** and release of the BOM groups (Na, $NH_{3\ (liq)}$)[20] from the

Scheme 5. Conversion of 21 into the Sato Lactone



resultant **23**. Treatment of the emerging diol **24** with TPAP-NMO[21] gave lactone **25** in high yield. Unlike related materials,[22] compound **25** readily formed an enolate[23] (LDA), enabling oxygenation with the Davis oxaziridine.[24] This led to a product consisting of a 7:3 mixture of substance **26** (thus obtained in 24 steps from commercial phenol **5**) and unreacted **25**. This mixture was best advanced to the following step, MOM protection of the free OH group, without separation of the two components. This transformation failed when attempted under customary conditions (MOM-Cl, Et_3N), but deprotonation of **26** (NaHMDS) and reaction of the presumed N,O-dianion intermediate with MOM-Cl smoothly produced **27**. No trace of epimeric byproducts could be detected by high-field NMR, reflecting the inaccessibility of the proton at the α-position of the carbonyl group in **25** and **27**. The latter was thus obtained in 49% yield after chromatography, together with unreacted **25** (33%). The subsequent desilylation of **27** afforded **28** contaminated with ca. 25% of isomeric lactone **29** (Figure 1). The mixture of the two lactones was used as such in the following step: the release of the BOC group. This operation was best carried out by heating to 215 °C.[25] A compound that was spectroscopically identical (^{1}H NMR, IR) to the Sato lactone thus emerged. This material was accompanied by a small amount of byproduct **30**, the structure of which was ascertained by X-ray diffractometry.[26]

On the other hand, the NMR spectra of the Sato lactone (both the published ones and the identical ones obtained by us) were inconsistent with structure **22**, but in excellent accord with isomeric constitution **31** (Figure 1). Key pieces of evidence in support of this structural correction are as follows. First, the ^{1}H NMR spectrum of the compound in $CDCl_3$ exhibits a sharp doublet at 2.91 ppm (1H, J = 12 Hz) and a doublet of doublets at 3.80 ppm (1H, J_1 = 12 Hz, J_2 = 5 Hz). The 2D-COSY spectrum of the same solution shows that the doublet at 2.91 ppm correlates only with the doublet of doublets at 3.80 ppm. Furthermore, shaking the NMR solution wih D_2O causes disappearance of the doublet at 2.91 ppm and collapse of the doublet of doublets at 3.80 ppm into a doublet, J = 5 Hz. Thus, the doublet at 2.91 ppm is produced by an OH

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group coupled to a single vicinal proton. This is inconsistent with structure **22**, but in accord with **31**.

An X-ray diffractometric study[26b] conclusively proved that the presumed **22**, as obtained both by Sato and by us, is in fact **31**. A noteworthy feature of the solid-state structure of the molecule (Figure 2) is that both six-membered rings are in a

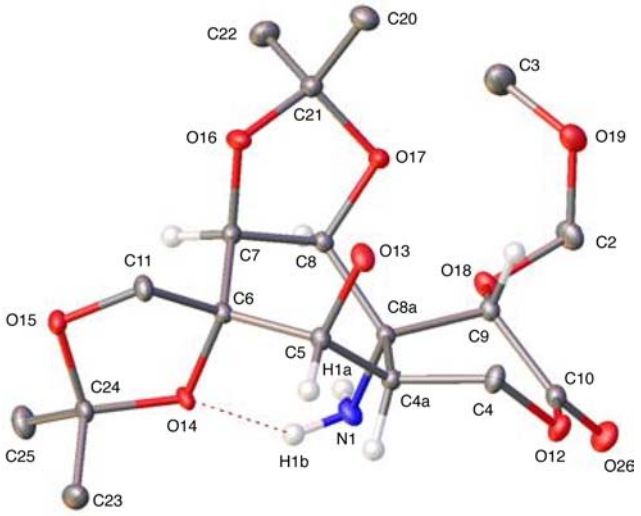
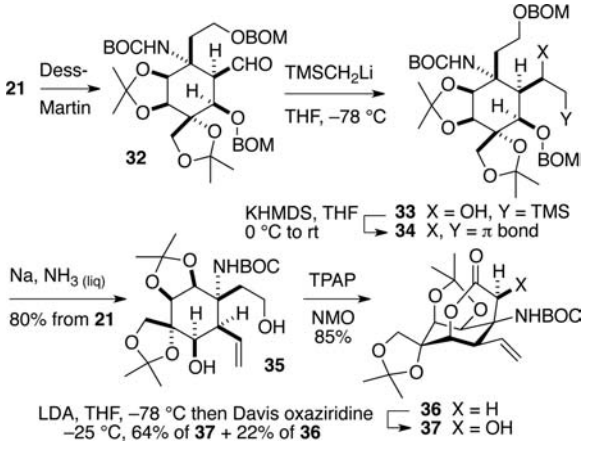


Figure 2. X-ray structure of actual Sato lactone, **31**.

boat-like conformation. An intramolecular hydrogen bond exists between the *pro*-(*R**) H of the amino group and the C-6 oxygen atom, while an intermolecular one occurs between the C-5 OH of one molecule and the lactone carbonyl of a second one.[27]

The fact that Sato and co-workers obtained synthetic **1** from **31** suggests that more advanced derivatives thereof must isomerize back to TTX-like structures. Regardless, the newly uncovered structural discrepancy induced us to place our claim of a formal synthesis of (±)-**1** on a more secure basis. Alcohol **21** was thus elaborated to the racemate of the Du Bois TTX intermediate, **37** (Scheme 6).[3d] Dess-Martin oxidation gave aldehyde **32**, which again reacted poorly under Wittig conditions, but it successfully afforded **34** upon Peterson olefination. Release of the BOM groups and TPAP-NMO oxidation of the resultant **35** furnished **36**, which, as in the case

Scheme 6. Conversion of 21 into Racemic DuBois Tetrodotoxin Intermediate, 37



of **25** before, underwent smooth hydroxylation to **37** under Davis conditions. The structure of **37** is secure,[3d] but as an extra precaution, it was confirmed by X-ray diffractometry.[26b]

Lactone **37** has been converted into TTX in four steps.[3d] The sequence just detailed thus amounts to a formal synthesis of (±)-**1** in 30 steps from commercial **5**. In terms of total number of steps from commercial materials,[28] the present avenue to TTX is competitive with known alternatives.[29]

The work presented herein illustrates a first synthetic application of the bimolecular oxidative amidation of phenols, intramolecular variants of which have been key, in the past, to syntheses of various nitrogenous natural products.[5] Moreover, it provides additional evidence that oxidative amidation methods can sustain the synthesis of fairly complex molecules, even when incorporated at an early stage of the sequence leading to the target. The structural correction of the Sato lactone may lead to new strategies for future syntheses of **1** based on fused, rather than bridged, bicyclic intermediates. Improvements of the route disclosed here and transposition of these findings to an enantiocontrolled avenue to TTX are being researched and will be the subject of future reports.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray crystal structures of compounds **30**, **31**, and **37**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00935.

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Notes

The authors declare no competing financial interest.

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(10) The following minor modification of the published procedure (ref 8) was beneficial: instead of application of an aqueous workup, the crude reaction mixture was concentrated under reduced pressure and the residue was directly applied to a silica gel column, which was then eluted with 10% EtOAc in hexanes. Several runs of this reaction gave yields ranging from 40% to 50%, making the average yield 45%.

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(18) Within the limits of 300 MHz ^{1}H NMR, this step produced only the correct diastereomer of the diol. Interestingly, Alonso and collaborators reported weak and opposite diastereoselectivity in an analogous reaction of a structurally related substrate: See ref 4d.

(19) The $LiBH_4$ reduction step also afforded variable quantities (10−20%) of a byproduct, tentatively identified as arising from transfer of one BOC group from the bis-BOC amide to the NHBOC group. The presumed structure of this material is rendered in the Supporting Information as compound **A**.

(20) Hydrogenolytic methods produced unsatisfactory results in the present case, but efficient deprotection was achieved with Na/$NH_{3\ (liq.)}$.

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(22) See the behavior of compound **49** in ref 3c.

(23) Verified by > 95% D incorporation at the α-C═O *exo* position upon quenching with D_2O. Furthermore, treatment of the resultant monodeutero derivative with LDA and then water returned **25**, indicating that (i) only the α-C═O *exo* proton is abstractable and (ii) only the β-face of the enolate is accessible to incoming electrophiles.

(24) Review: (a) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (b) The oxaziridine was prepared according to: Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.

(25) BOC release under Du Bois conditions (ref 3d as well as: Hinman, A. Dissertation, Stanford University, 2004) was unsatisfactory with this substrate.

(26) (a) The X-ray structure of **30** also validated the structure of all prior intermediates. (b) See Supporting Information for details of this X-ray study.

(27) An MM+ calculation (HyperChem package) suggests that **31** is more stable than **22** by ca. 4.6 kcal/mol.

(28) By way of comparison, Kishi prepared (±)-**1** in 31 steps (refs 3a, b) and Sato in 33 steps (ref 3f) from commercial starting materials. A comparison between the present effort and routes to (−)-**1** is not meaningful; still, the landmark Du Bois synthesis (ref 3d) involves 33 steps from isoascorbic acid; the Sato one, 33−34 steps from glucose (refs 3g, h); and the Isobe one, 34 steps from glucosenone (ref 3e as well as: Satake, Y.; Nishikawa, T.; Hiramatsu, T.; Araki, H.; Isobe, M. *Synthesis* **2010**, *12*, 1992).

(29) An unusually concise alternative might be possible through appropriate modifications of the Alonso route (refs 4c−4d), which in its present form yields advanced intermediates that may not be easily deprotectable at late stages of the synthesis (cf. the methyl orthoesters **13** in ref 4d). The crucial importance of end-game deprotection strategies is especially apparent in the work of Isobe (refs 3c, 3e, and 4b).

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