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Approach to Tetrodotoxin via the Oxidative Amidation of a Phenol

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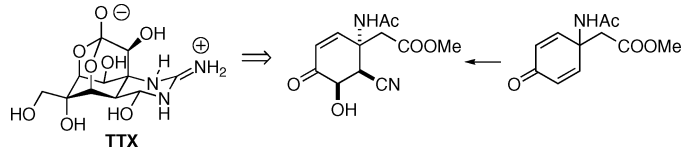
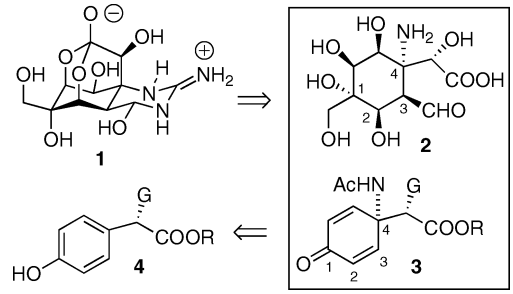
ABSTRACT



An approach to tetrodotoxin that relies on the oxidative amidation of methyl 4-hydroxyphenylacetate as a key step is described. The stereoselective introduction of a β-hydroxynitrile functionality on one of the double bonds of the emerging dienone is achieved through an intramolecular nitrile oxide cycloaddition−fragmentation sequence.

Tetrodotoxin (TTX, **1**, Scheme 1),[1] a potent neurotoxin,[2] is one of the classical targets in synthetic organic chemistry. Following Kishi's historical conquest of **1** in 1972,[3] interest in alternative approaches waned,[4] but a resurgence of activity in this domain has occurred in recent years as a consequence of landmark total syntheses by Isobe (from carbohydrate educts)[5] and DuBois (through a remarkable C−H insertion of a nitrenoid to install a key N atom).[6] Such accomplishments have inspired additional syntheses[7] and synthetic studies.[8]

Scheme 1. Retrosynthetic Hypothesis for Tetrodotoxin



Indeed, the intricate structure of TTX provides limitless opportunity for the exploration of uncharted strategies. In that respect, we recognized the possibility apparent in the retrosynthetic diagram of Scheme 1. Compound **3**, which is the product of oxidative amidation[9] of phenol **4** (G =

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(5) (a) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (b) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782. (c) Urabe, D.; Nishikawa, T.; Isobe, M. *Chem. Asian J.* **2006**, *1*, 125. (d) Isobe, M.; Ohyabu, N.; Nishikawa, T. *Yuki Gosei Kagaku Kyokaishi* **2007**, *65*, 492.

(6) Hinman, H.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

(7) (a) Sato, K.-I.; Akai, S.; Shoji, H.; Sugita, N.; Yoshida, S.; Nagai, Y.; Suzuki, K.; Nakamura, Y.; Kajihara, Y.; Funabashi, M.; Yoshimura, J. *J. Org. Chem.* **2008**, *73*, 1234. (b) Sato, K.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496.

(8) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768.

(9) (a) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175. (b) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. Review of oxidative amidation chemistry: (c) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M; Chang, J; Chai, D. *Synthesis* **2007**, 3759.

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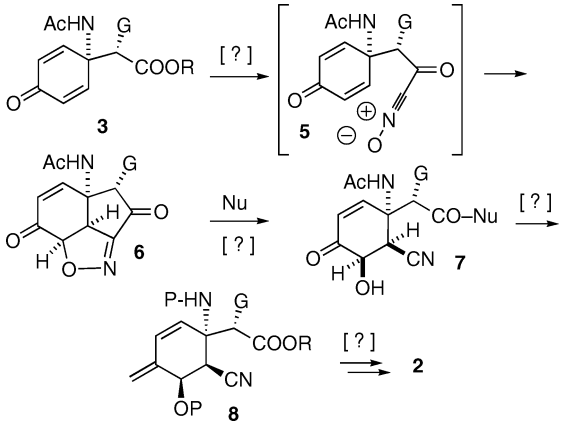
appropriate oxygen functionality or precursor thereof), nicely maps onto intermediate **2**, which emerges upon release of the ortholactone and guanidine moieties in **1**. The elaboration of **3** into **2** requires, inter alia, the stereocontrolled introduction of an OH group at C-2 and of a CHO group (or an equivalent functionality) at C-3. The work of Fukuyama[10] suggests that such a goal may be attained via an intramolecular nitrile oxide cycloaddition (INOC) reaction[11] followed by isooxazoline fragmentation, leading to the installation of a cyano group as a formyl equivalent.

The implementation of such a strategy in the context of **3** entails the seemingly straightforward sequence seen in Scheme 2. In fact, this planned course of action comports a

Scheme 2. Strategy for the Elaboration of **3** into **7**



nettlesome issue relating to the viability of the keto-isooxazoline **6**. The CAS database records no examples of substructures **9** or **10** (Figure 1), although 19 occurrences of

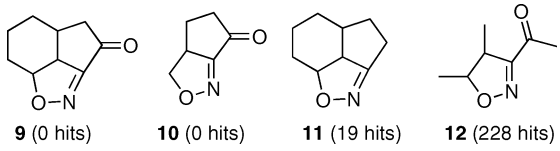
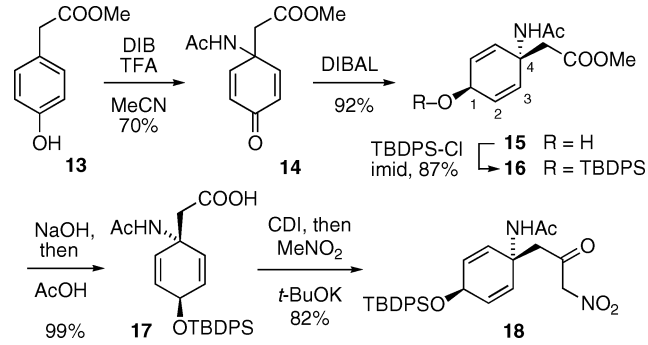


Figure 1. CAS search for substructures **9**−**12**.

its "des-keto" analogue **11** are found[12] and more than 200 keto-isooxazolines of the general type **12** are known. Concern regarding **6** emanates from the fact that its C═O group is forced into a nearly eclipsed orientation relative to the C═N bond.[13] The ensuing repulsive electrostatic interactions[14] may well engender unusual reactivity and possibly instability. In any event, nucleophilic cleavage of the isooxazoline should produce **7**, which we imagined to progress to **8** and hence to **2** via a stereocontrolled osmylation of the diene system. In this paper, we describe exploratory studies that defined a method to elaborate an intermediate of the type **3** into one such as **7** according to the format of Scheme 2. For the purpose of this model investigation, group G was chosen as H.

The starting point of this research was phenol **13**, the reaction of which with *I*,*I*-(diacetoxy)iodobenzene ("DIB") in MeCN containing 1.5 equiv of trifluoroacetic acid[9b] afforded **14** in 70% yield (Scheme 3). In preparation for the

Scheme 3. Preparation of a Nitroketone Substrate for INOC



advancement of the ester function to an α-nitroketone,[15] a precursor of reactive intermediate **5** (Scheme 2), the dienone carbonyl was selectively reduced (DIBAL) and alcohol **15** was silylated. Such a maneuver suppressed the possibility of later Michael cyclization of the nitroketone. Compound **16** emerged as the major component of an 11:1 mixture of C-1 epimers. Its relative configuration was assigned on the basis of an X-ray crystallographic study of a later intermediate (vide infra).

Saponification of the ester and careful acidification (AcOH) afforded acid **17**, a sensitive material that cyclized readily to lactone **19** (Scheme 4), a synthetic dead end, in media with a pH lower than about 2. Activation of the acid with carbonyldiimidazole ("CDI")[16] and condensation of the

(10) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323.

(11) Reviews: (a) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, Germany, 1990; Vol. I, p 77. (b) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. See especially p 12255−12259.

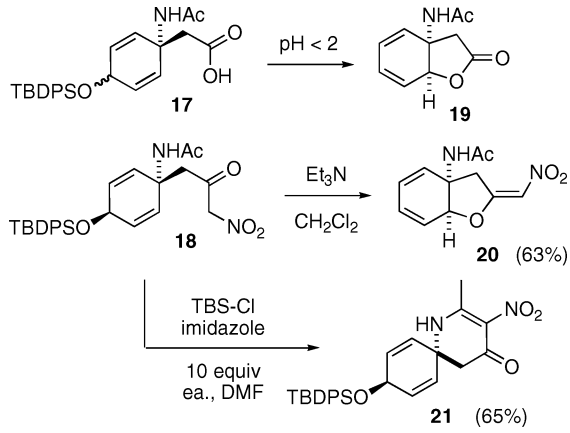
(12) Representative examples: ref 10 as well as: (a) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (b) Tsantali, G. G.; Dimtsas, J.; Tsoleridis, C. A.; Takakis, I. M. *Eur. J. Org. Chem.* **2007**, 258. (c) Gao, S.; Tu, Z.; Kuo, C.-W.; Liu, J.-T.; Chu, C.-M.; Yao, C.-F. *Org. Biomol. Chem.* **2006**, *4*, 2851. (d) Fernandez-Mateos, A.; Pascual Coca, G.; Rubio Gonzalez, R. *Tetrahedron* **2005**, *61*, 8699. (e) Yeh, M.-C. P.; Jou, C.-F.; Yeh, W.-T.; Chiu, D.-Y.; Reddy, N. R. K. *Tetrahedron* **2005**, *61*, 494. (f) Souza, F. E. S.; Rodrigo, R. *Chem. Commun.* **1999**, 1947. (g) Toyota, M.; Asoh, T.; Fukumoto, K. *Heterocycles* **1997**, *45*, 147. (h) Stannsen, D.; De Keukeleire, D.; Vanderwalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 547. (i) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 979. (j) Curran, D. P.; Jacobs, P. B. *Tetrahedron Lett.* **1985**, *26*, 2031.

(13) The N═C−C═O dihedral angle in an MM$^+$-optimized structure **6** where G = H is $q = -17.0°$.

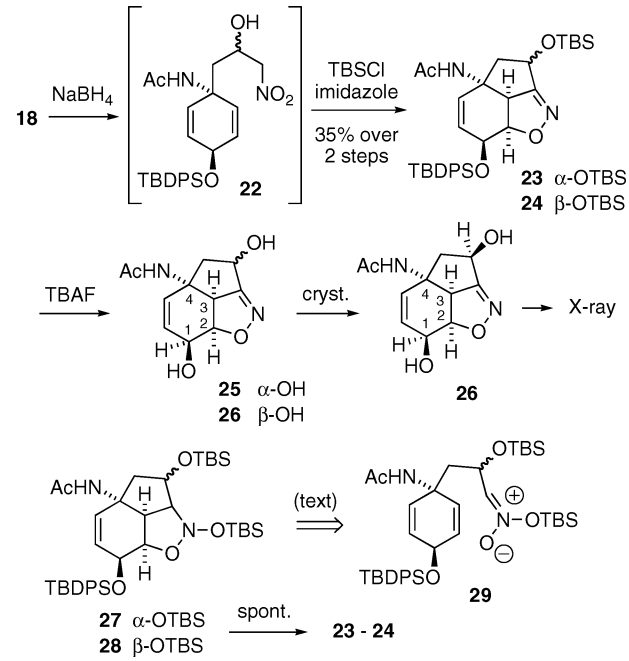
(14) Similar (but not identical) electrostatic forces seemingly define the unusual conformational properties of *N*-acyl piperazic acids: (a) Xi, N.; Alemany, L. B.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 80. (b) Ciufolini, M. A.; Xi, N. *Chem. Soc. Rev.* **1998**, 437.

(15) Chemistry of α-nitroketones: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Tetrahedron* **2005**, *61*, 8971.

Scheme 4. Undesired Reactions of Intermediates **17** and **18**



Scheme 5. Cyclization of Reduced Derivatives of **18**



resultant acid imidazolide with CH_3NO_2/*tert*-BuOK[17] provided nitroketone **18**.[18]

The dehydration of **18** to the corresponding α-keto-nitrile oxide[19] proved to be troublesome. Various reagents commonly used for this purpose, such as 4-chlorophenyl isocyanate[20] and BOC_2O,[21] performed poorly, affording the desired INOC product as a minor component of a complex mixture. Exposure of **18** to Et_3N[22] also failed to induce cycloaddition, promoting instead conversion into **20** (Scheme 4; structure ascertained by X-ray crystallography), a compound that formally arises through O-alkylation of the enolate of the nitroketone via allylic displacement of the OTBDPS group.

Sensing that such obstacles may be a consequence of the difficulties alluded to earlier, we sought to alleviate the problem by reducing the keto group prior to the INOC step. Accordingly, $NaBH_4$ treatment of **18** provided alcohol **22** (Scheme 5), a sensitive material that was prone to undergo retro-Henry fragmentation, especially upon attempted purification. Therefore, crude **22** was immediately O-silylated (TBSCl/imidazole/Et_3N). This step occurred with a concomitant Torssell-type cyclization[23] to a 1:1 mixture of isooxazolines **23** and **24**. Such a lack of diastereoselectivity signals that the steric demand of an OTBS group is insufficient to exert stereocontrol during the cycloaddition step. This is contrary to the case of a tosylamide.[12a] It is worthy of note that a mixture of diastereomeric nitroso acetals[24] **27** and **28** was also isolated as a minor product of the reaction (flash chromatography). Upon standing, **27** and **28** underwent spontaneous conversion into **23** and **24**. A sample of nearly pure diastereomer **28** (6% yield) was secured by flash chromatography and characterized. This material was converted into **24** upon standing. Such observations implicate the intermediacy of siloxy nitronate[25] **29** en route to the isooxazolines, i.e, product formation via an intramolecular siloxynitronate−olefin cycloaddition (ISOC) process. It remains unclear whether the ISOC pathway operates exclusively or in parallel with the INOC one.

Release of the silyl ethers from **23** and **24** afforded a 1:1 mixture of diols **25** and **26**. Crystals of pure **26** slowly separated from this mixture, enabling an X-ray structural study that ascertained the relative configuration between C-1 and C-4. Recall that this stereochemical relationship had been established upon DIBAL reduction of **14** (Scheme 3).

The success of the TBSCl-mediated cyclization of **22** induced us to attempt the same reaction with ketone **18**. Treatment with 1 equiv each of TBSCl and imidazole induced slow cyclization to **30**, which was obtained in 38% yield after chromatography. At this time, we are unable to resolve the question of whether **30** forms via an ISOC or an

(16) (a) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351. Review: (b) Armstrong, A.; Li, W. N,N'-Carbonyldiimidazole. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley, 2006. http://www.mrw.interscience.wiley.com/eros/articles/rc024/frame.html; DOI 10.1002/047084289X.rc024.pub2.

(17) Baker, D. C. Putt, S. R. *Synthesis* **1978**, 478. See also ref 15.

(18) The synthesis of **18** detailed herein was devised by Dr. Cyril Benhaim during his tenure as a postdoctoral fellow in this group. We thank Dr. Benhaim for his efforts in this area.

(19) These species are documented; e.g.: (a) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1962**, 2215. (b) Martin, S. F.; Dappen, M. S.; Dupré, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209. For the ester and nitrile analogues, see: Kozikowski, A. P.; Adamcz, M. *J. Org. Chem.* **1983**, *48*, 366.

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(21) Basel, Y.; Hassner, A. *Synthesis* **1997**, 309.

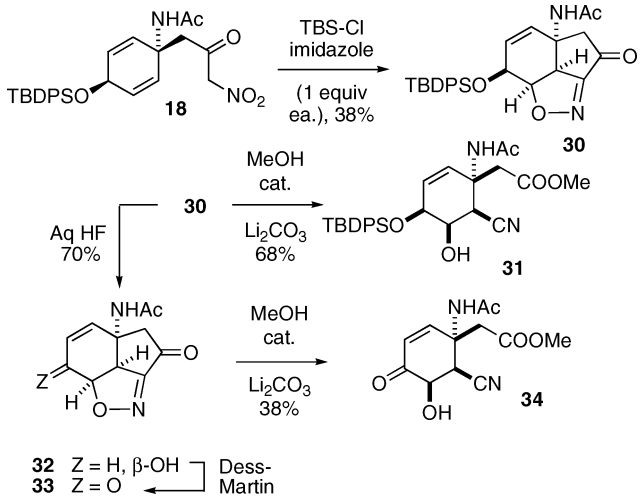
(22) Cecchi, L.; De Sarlo, F.; Marchetti, F. *Tetrahedron Lett.* **1985**, *46*, 7877.

(23) (a) Andersen, S. H.; Das, N. B.; Joergensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta. Chem. Scand. B* **1982**, *36*, 1. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988.

(24) Chemistry of nitroso acetals: Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593, and refs cited therein.

(25) See ref 23 as well as (a) Klebe, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 3399. (b) Shitkin, V. M.; Ioffe, S. L.; Kashutina, M. V.; Tartakovskii, V. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 2266. (c) Namboothiri, I. N. N.; Hassner, A.; Gottlieb, H. E. *J. Org. Chem.* **1997**, *62*, 485.

Scheme 6. Preparation and Methanolysis of Keto-Isooxazolines



INOC mechanism. Remarkably, attempts to accelerate this reaction by the use of excess reagents (10 equiv each) resulted in the unexpected formation of the noteworthy dihydropyridone **21** as the major product (Scheme 4, 65% after chromatography) and in a concomitant decrease in the yield of **30** (5% after chromatography). The structure of this architecturally unique material (the CAS database contains no records of like substances) was ascertained by X-ray crystallography. The compound formally arises through an unusual Knoevenagel-type condensation of the nitroketone with the acetamide, proceeding in all likelihood via an O-silyl imino ether derivative of the latter unit.

At this juncture, we refocused our attention on the development of a procedure for keto-isooxazoline ring fragmentation. Once again, the execution of the desired transformation required a good deal of experimentation. Initial attempts to induce conversion of **30** into **31** by the action of NaOMe/MeOH or K_2CO_3 in alcohols (MeOH, EtOH, BnOH) gave disappointing results. Methanolic imidazole or 4-dimethylaminopyridine had no effect on the substrate. It ultimately transpired that a catalytic amount of Li_2CO_3 in MeOH performed best, promoting conversion of **30** into **31** in 68% yield after chromatography.

Finally, compound **33**, an analogue of **6** where G = H, was prepared by desilylation of **30** and ensuing Dess−Martin oxidation. Substance **30** was quite intolerant of TBAF or the HF−pyridine complex: either reagent, especially the basic TBAF, rapidly degraded it. Conversely, it readily withstood the action of aqueous HF in MeCN, which provided **32** in 70% yield. Diketone **33** was not amenable to chromatographic purification (poor recovery), and it was best advanced to the next step in crude form. Thus, exposure to cat. Li_2CO_3 in MeOH furnished the target **34** in 38% yield after chromatography (Scheme 6).

This work demonstrates the feasibility of the planned approach to TTX building blocks of type **7** along the lines of Scheme 2. It also provides information concerning the reactivity of a number of structurally novel intermediates. Ongoing research aims to parlay these findings into a total synthesis of **1**. Results of such investigations will be disclosed in due course.

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Supporting Information Available: Experimental procedures and characterization data for the compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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