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A Cascade Annulation Based Convergent Approach to Racemic Tetrodotoxin

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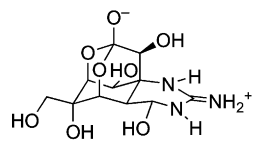
The synthetic power of the recently developed cascade annulations of β-(hetero)aryl-α-nitro-α,β-enals with the pyrrolidine-derived enamine of 2,2-dimethyl-1,3-dioxan-5-one is demonstrated by the first convergent route to (±)-tetrodotoxin.

Introduction

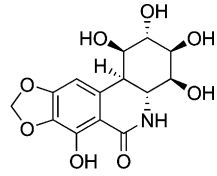
Complex structures and multiple stereocenters are common features of privileged natural products with potent biological properties, unique mechanisms of action, and potential (therapeutic) value. The synthesis of these compounds (or of appropriate derivatives) on a scale suitable for general demand (i.e., to analyze their properties fully and to develop their uses, as drugs, probes, sensors, etc.) currently require increased levels of efficiency. To that end, synthetic approaches based on multistep transformations, in which several bonds and stereocenters are generated in a one-pot fashion to gain rapid access to molecular complexity, are highly sought-after.[1]

A case in point is that of tetrodotoxin (Figure 1), a compound that captured the interest of researchers from a variety of disciplines right from its discovery.[2] Biological interest was due to its exceptional potency and the selectivity of the toxin in blocking voltage-gated sodium channels. By virtue of this property,[3] tetrodotoxin was instrumental in the identification, isolation, purification, and subsequent sequencing of the main protein subunit of these channels,[4] and remains widely employed in biological studies.[5,6] The pharmacological significance of tetrodotoxin, already discussed by Mosher in 1986,[7] is currently the subject of study in the fields of analgesia (for severe cancer and neuropathic opioid-refractive pain relief), drug-addiction withdrawal treatment, and local anesthesia.[8,9]

For chemists, the toxin was initially a challenging structural problem, which was simultaneously and independently solved by four research groups.[10] Afterwards, tetrodotoxin represented a most demanding synthetic goal, first conquered for the racemic mixture in 1972 by Kishi and coworkers,[11,12] and only recently, with the turn of the century, in enantiopure form, by the research groups led by Isobe, Du Bois, Noheda, and Sato.[13,14]



Tetrodotoxin
(Na-channel blocker)



Pancratistatin
(antitumoral)

Figure 1. Tetrodotoxin and pancratistatin: representative members of two families of natural products containing nitrogen-bearing polyoxygenated cyclohexane components.

Although the reported syntheses are remarkable achievements, they allow the preparation of the toxin, as well as of some natural analogues and new synthetic derivatives, only in limited amounts. Further advancements toward practical access will certainly depend on our ability to improve the efficiency of syntheses of highly oxygenated nitrogen-bearing cyclohexanes,[15] a key structural unit of the TTX family [and of other families of complex natural products as well, including that represented by the antitumoral pancratistatin (Figure 1)].

In this context, we have recently developed a new procedure[16] in which protected aryl- or heteroarylnitrocyclitols of type **C** (Scheme 1), fully functionalized cyclohexanes with five stereogenic centers, are assembled in a one-pot procedure through cascade annulations of β-(hetero)aryl-α-nitro-α,β-enals (**A**), a rare and essentially unexplored type of compounds,[17] with the pyrrolidine-derived enamine of 2,2-dimethyl-1,3-dioxan-5-one (**B**). In the same communication we also reported the conversion of one of the aryl-substituted nitrocyclitols into a pancratistatin analogue to illustrate the value of the new annulation protocol.

We have now addressed the more difficult case of TTX in order both to challenge the methodology with a more demanding target and to evaluate the potential of the annulated products as synthetic intermediates for more than one family of natural products.

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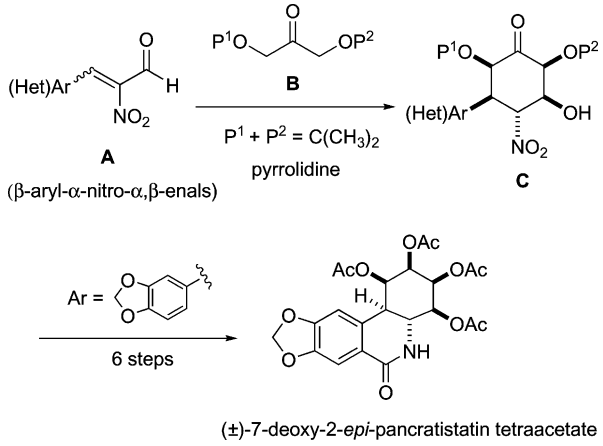


Scheme 1. One-pot annulation producing the protected nitrocyclitols **C** and its application to a short and practical synthesis of a pancratistatin analogue (see ref.[16]).

In the event, a novel and shorter pathway to TTX based on the development of a robust large-scale synthesis of a furfural-derived furyl-nitrocyclitol of type **C** and its conversion into a known toxin intermediate was achieved.

Results and Discussion

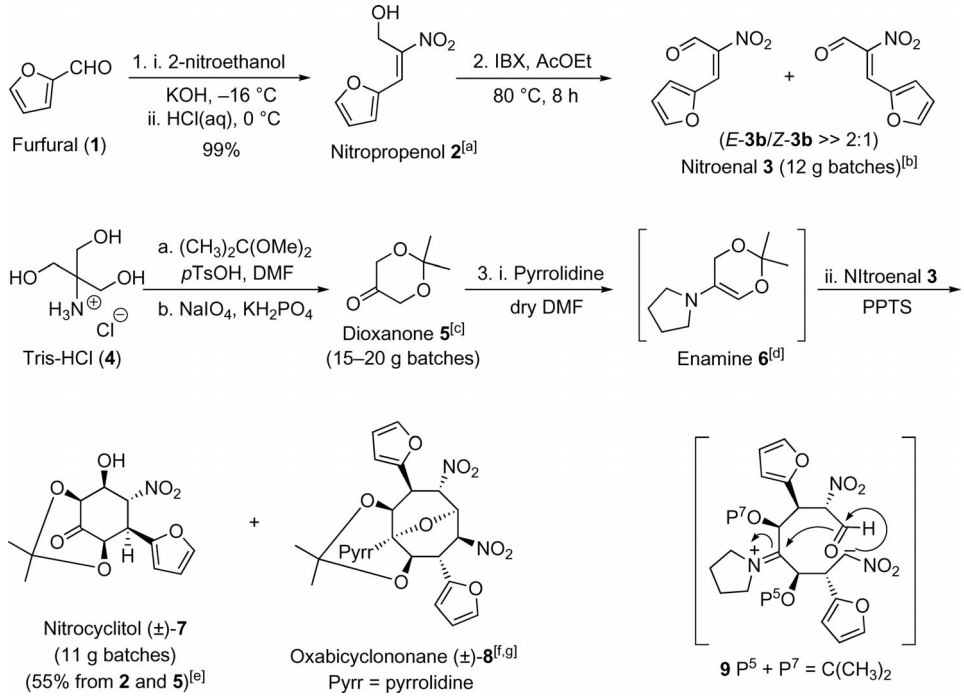
In the case of TTX, in relation to those of pancratistatin and related *Amaryllidaceae* constituents, correct selection of the nitrocyclitol precursor and the capacity to prepare it on large scales in a reliable and easy manner appeared to be much more critical issues in terms of practicability, particularly because the higher structural complexity of TTX would call for a larger number of synthetic operations once the key cyclohexane ring had been assembled.

The nitrocyclitol **7** (Scheme 2) looked appropriate for several reasons. First of all, its β-furyl-α-nitro-α,β-enal precursor **3** proved to be particularly stable, significantly more so than the corresponding aryl-derived nitroenal analogues.[17] Secondly, the preparation of **3** required furfural, a cheap and renewable source, as starting material. Additionally, the furyl group in **7** would most likely serve well as precursor of the (masked) formyl group the TTX molecule has at position C-4.

Large-Scale Preparation of the Protected Cyclohexitol 7

We initiated our study by scaling up the preparation of the cyclohexitol **7** through the pyrrolidine-promoted annulation of 3-(furan-2-yl)-2-nitroacrylaldehyde (**3**) and 2,2-dimethyl-1,3-dioxan-5-one (**5**), a process we had carried out at the 80–130 mg scale and in 24–38% yields (Scheme 2).

We began by preparing the nitroenal **3** as recently described, but we were now able to do so in 12 g batches, by condensation of furfural (**1**, 7 mL) with 2-nitroethanol to form the nitropropenol **2** (99%), followed by oxidation with 2-iodoxybenzoic acid (IBX).[18,19] Although the dioxanone **5** is commercially available, it is expensive; therefore, we also



Scheme 2. Practical synthesis of the protected cyclohexitol **7**.[21] [a] Represented as its most stable conformer; see ref.[17] [b] For a detailed experimental procedure, see the Supporting Information; see also ref.[17,18] [c] For experimental procedures, see ref.[20] [d] For a GC–MS analysis, see the Supporting Information. [e] For a detailed procedure, see the Experimental Section. [f] Obtained in as much as 10% yield under the conditions reported in ref.[16] (see also the Experimental Section); barely formed, mixed with other faster running complex unidentified side products, under the improved conditions reported here for the preparation of **7** (see the main text and the Supporting Information). [g] For an X-ray structure, see the Supporting Information.

prepared it in multigram batches by oxidative cleavage of the acetonide of 2-amino-2-(hydroxymethyl)propane-1,3-diol hydrochloride (Tris-HCl, **4**).[20] None of the nitropropenol **2**, the nitroenal **3**, or the dioxanone **5** required chromatography: the nitropropenol **2** and the nitroenal **3** were directly used for the next step after extraction or filtration, respectively, of the cooled reaction mixture and evaporation of the solvent, whereas dioxanone **5** was purified by vacuum distillation.

With sufficient quantities of **3** and **5** to hand, we next studied their gram-scale annulation to **7**, which proved feasible and reproducible under the conditions previously reported.[16] However, better yields were obtained when the reaction was run at room temp. instead of at 0 °C and when PPTS was added not initially, but mixed with the nitroenal **3** to the preformed enamine **6** derived from pyrrolidine and the dioxanone **5**. In practice, we consistently prepared batches of about 11 g of the nitrocyclitol **7** (55% from **2** and **5**), each batch taking 5 man working-days including the synthesis of the two annulation partners – the nitroenal **3** and the dioxanone **5** – and the preparation of IBX required for **3** (Scheme 2).[21]

Remarkably, for the entire process we needed just a single, easy-to-perform chromatographic separation, most favorably in the last step, to separate the final product **7** from some dark material that remained attached to the column and from some minor faster running eluates.[22]

The protected nitrocyclitol **7** was the single major product from the reaction between the nitroenal **3** and the dioxanone **5**. In fact, **7** was the only six-membered α,α′-annulated dioxanone we identified (even when performing the annulation reaction on a large scale), illustrating the exquisite stereocontrol with which the five stereocenters in **7** are generated during the formal [3+3] annulation process.

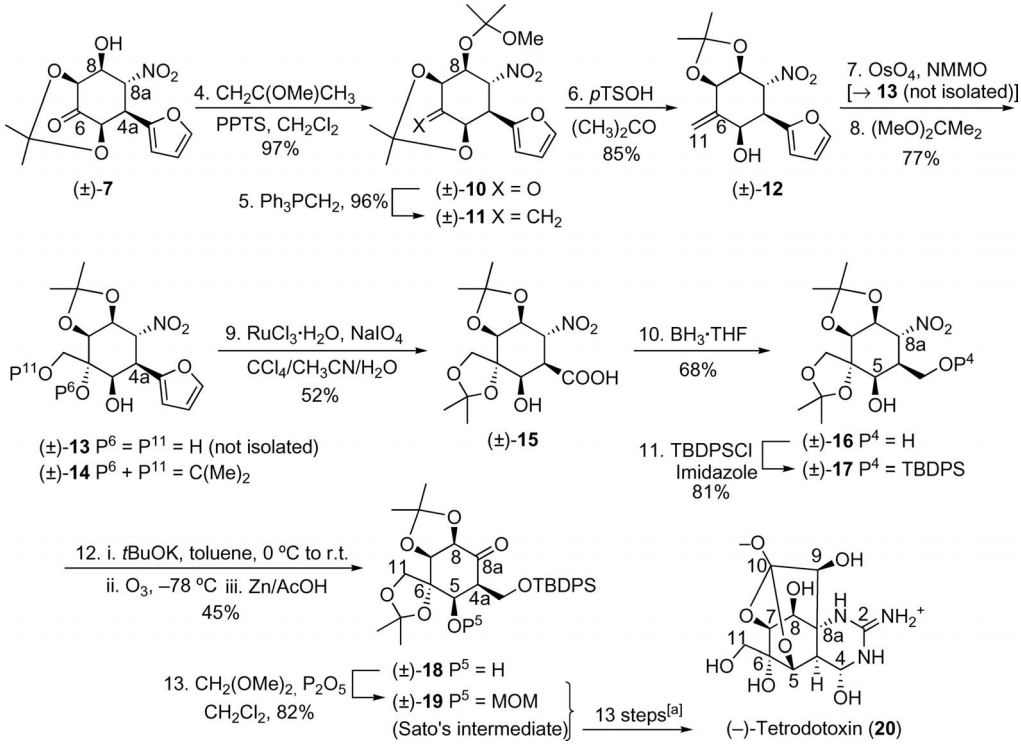
Among those minor reaction products significantly less polar than **7**, we were able to isolate an additional α,α′-annulated dioxanone, containing an eight-membered – rather than a six-membered – carbocycle and identified as compound **8** (Scheme 2).

Notably, every ring carbon atom in **8** is stereogenic and functionalized: two with carbon substituents (furyl rings), two other with nitrogenated substituents (nitro groups), and the other four with oxygen (three at the alcohol and the fourth at the ketone oxidation stage).

In fact, compound **8** is a 9-oxabicyclo[3.3.1]nonane; its formation could be formally explained in terms of the addition of one molecule of the enamine **6** to two molecules of the nitroenal **3** with loss of one of the two formyl groups.[23] This would afford the putative intermediate **9**, which would then evolve through an intramolecular Henry reaction and subsequent aminal formation.

From the Nitrocyclitol 7 to Sato's Intermediate 19

To establish the validity of our methodology for the preparation of tetrodotoxin (i.e., the capability of an assembled nitrocyclitol of type **C** to serve as a synthetic precursor of the toxin), we next worked on the transformation of **7** to **19** (Scheme 3), itself an advanced intermediate recently established by Sato and co-workers.[13e]



Scheme 3. Conversion of **7** into Sato's intermediate (TTX numbering is used) **19**. [a] See ref.[13e]

Conversion of **7** into **19** would essentially require, besides some deprotection/protection steps, three main operations: elaboration of its C-6 oxo group into the acetonide-protected dihydroxylated C-6–C-11 subunit, oxidative conversion of its furyl ring into the silyl ether of the C-4a hydroxymethyl group, and transformation of its C-8a nitro substituent into a ketone.

In practice, such a transformation was far from trivial. In fact, the densely functionalized nature of the intermediates made necessary a significant amount of explorative labor to find the right protective groups, reaction conditions, and order of operations. Finally, the working pathway of **7** to **19** described below was established.

In the event, the introduction of C-11 was carried out, after protection of the C-8 hydroxy group of **7** in the form of the mixed acetal **10**, by Wittig methylenation. This afforded **11**, which proved highly reluctant to undergo oxidation at the exocyclic double bond. Acid-induced modification of the protection pattern of **11** gave **12**, the double bond of which was exclusively dihydroxylated from the less hindered face, as confirmed by X-ray analysis of **14** (the diacetonide of the non-isolated diol intermediate **13**).

Formation of the *tert*-butyldimethylsilyl ether of the C-4a hydroxymethyl group was accomplished by a three-step sequence: ruthenium-mediated oxidation of **14** to the β-hydroxy acid **15**,[24] reduction (borane) to the diol **16**, and final selective protection of the primary hydroxy group to afford the silyl ether **17**.

The two final steps of the sequence – the transformation of the nitro group of **17** into the carbonyl group of **18** (by ozonolysis of the corresponding nitronate intermediate) and the subsequent protection of the C-5 hydroxy group as its methoxymethyl ether – were carried out under conditions employed for similar substrates. The obtained tetrodotoxin intermediate **19** showed characterization data identical to those previously described.[13e]

Conclusions

The 11 g batch preparation of the protected nitrocyclitol **7** and its capability to give access to Sato's advanced intermediate **19** in racemic form in just 13 steps [and hence, formally, to (±)-tetrodotoxin in only 26 steps], illustrate, respectively, the practicability of the formal [3+3] annulations of β-heteroaryl-α-nitro-α,β-enals and the versatility of their products – the highly functionalized nitrocyclohexitols – to serve well as synthetic precursors for several families of complex natural products containing polyoxygenated cyclohexanes as substructural units.

Work to understand the intimate details of the annulation process and to develop its potential further is in progress; in particular, we are exploring enantioselective versions of the annulation step as well as new pathways to TTX either from **19** or from other structurally related protected nitrocyclitols.

Experimental Section

Gram-Scale Synthesis of (1*S,5*R**,6*R**,7*R**,8*S**)-6-(2-Furyl)-8-hydroxy-3,3-dimethyl-7-nitro-2,4-dioxabicyclo[3.3.1]nonan-9-one (7):** An oven-dried 2 L round-bottomed flask was sequentially charged with the dioxanone **5** (9.33 g, 71.8 mmol), pyrrolidine (4.8 mL, 57.4 mmol, 0.8 equiv.), and dry DMF (60 mL) at room temp. under argon and with magnetic stirring. After 10 min, anhydrous Na_2SO_4 (21.6 g, 152 mmol) was added. After 3 h, a solution of **3** [12.00 g, prepared from furfural (1 equiv.) through the nitropropenol **2** as described in the Supporting Information] and PPTS (3.60 g, 14.4 mmol, 0.2 equiv.) in dry DMF (300 mL) was added. After 2 h, the reaction mixture was diluted with an H_2O/EtOH mixture (1:4, 300 mL) and stirred for 12 h. The solvents were removed (rotary evaporator) to give a dark brown residue, which was chromatographed {the residue was dissolved in CH_2Cl_2 (ca. 200 mL), silica (50 g) was added, the solvent was removed (rotary evaporator) and the charged silica was added on the top of a glass column of 7 cm in diameter filled with silica (25 cm height) previously packed with the aid of AcOEt/hexane (3:7); eluent was AcOEt/hexane (3:7, 1 L to elute the less polar side products, R_f = 0.8, 5 g, usually in the first four fractions of 250 mL) and AcOEt/hexane [1:1, 1.5 L to elute **7**, R_f = 0.6 (in AcOEt/hexane 3:7), usually in 13 fractions (5th to 17th) of about 100 mL]}, to give **7** (11.8 g, 55%) as a chromatographically pure brown solid, which was normally dissolved in the minimum amount of CH_2Cl_2 and crystallized by addition of hexane to give a crop of **7** as a white solid [7.0 g, m.p. 190–199 °C (Et_2O/hexane), decomposition] that was used in the next reaction; the crystallization mother liquors from a number of different reaction batches were usually gathered together and rechromatographed. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38 (d, J = 1.8 Hz, 1 H), 6.39 (d, J = 3.3 Hz, 1 H), 6.35 (dd, J_1 = 3.3, J_2 = 1.8 Hz, 1 H), 5.33 (dd, J_1 = 11.6, J_2 = 9.5 Hz, 1 H), 4.55 (dd, J_1 = 2.4, $J_2 \approx$ 1.6 Hz, 1 H), 4.51 (dd, $J_1 \approx$ 2.4, $J_2 \approx$ 1.3 Hz, 1 H), 4.21 (ddd, J_1 = 10.6, $J_2 \approx$ 9.5, J_3 = 1.6 Hz, 1 H), 3.52 (dd, J_1 = 11.6, J_2 = 1.3 Hz, 1 H), 2.96 (d, J = 10.6 Hz, 1 H), 1.58 (s, 3 H), 1.51 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 205.2, 147.3, 143.1, 110.8, 108.9, 99.9, 89.0, 79.1, 77.0, 76.2, 44.3, 28.2, 25.4 ppm. LRMS (ESI-TOF): *m*/*z* (%) = 320.0 (46) $[M + Na]^+$, 298.1 (100) $[M + H]^+$, 245.1 (18). HRMS (ESI-TOF): calcd. for $C_{13}H_{16}NO_7$ $[M + H]^+$ 298.0927; found 298.0921.

Oxabicyclononane (±)-8: Annulation of **5** (1.5 g) and **3** (1.96 g) in DMF at 0 °C, by the general procedure previously reported,[16] afforded [together with **7** (0.914 g, 26%)], **8** as a white solid [0.547 g, 10%, R_f = 0.67 (AcOEt/hexane 30%), m.p. 112–124 °C (Et_2O)]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.31 (m, 2 H), 6.37–6.28 (m, 4 H), 5.37 (dd, J_1 = 12.0, J_2 = 3.7 Hz, 1 H), 5.06 (dd, J_1 = 12.0, J_2 = 4.7 Hz, 1 H), 4.95 (dd, $J_1 \approx$ 4.3, $J_2 \approx$ 4.3 Hz, 1 H), 4.73 (d, J = 3.7 Hz, 1 H), 4.47 (dd, J_1 = 12.0, J_2 = 10.1 Hz, 1 H), 4.32 (d, J = 10.1 Hz, 1 H), 4.09 (dd, J_1 = 12.0, J_2 = 3.7 Hz, 1 H), 3.07–2.94 (m, 4 H), 1.94–1.75 (m, 4 H), 1.50 (s, 3 H), 1.44 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.0, 148.0, 142.6, 142.4, 110.7, 110.6, 109.8, 108.9, 101.2, 86.9, 84.0, 81.0, 72.6, 71.8, 71.4, 45.0 (2 C), 40.7, 38.7, 30.7, 25.1 (2 C), 24.3 ppm.

(1*S,5*R**,6*R**,7*R**,8*S**)-6-(2-Furyl)-8-(1-methoxy-1-methylethoxy)-3,3-dimethyl-7-nitro-2,4-dioxabicyclo[3.3.1]nonan-9-one (10):** 2-Methoxypropene (0.97 mL, 10.10 mmol, 3 equiv.) and PPTS (84 mg, 0.36 mmol, 0.1 equiv.) were added under argon to a solution of **7** (1 g, 3.34 mmol) in dry CH_2Cl_2 (16.8 mL). After the mixture had been stirred at room temp. for 30 min, Et_3N (0.5 mL) was added, and the volatiles were removed (rotary evaporator). Column chromatography (silica gel, AcOEt/hexane 15%) gave **10** (1.207 g, 97%) as a white solid, R_f = 0.49 (AcOEt/hexane 20%), m.p. 137–

139 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37 (dd, J = 1.8, 0.7 Hz, 1 H), 6.41 (d, J = 3.3 Hz, 1 H), 6.35 (dd, J_1 = 3.3, J_1 = 1.8 Hz, 1 H), 5.45 (dd, J_1 = 11.7, J_2 = 9.6 Hz, 1 H), 4.69 (dd, J_1 = 1.9, J_2 = 1.9 Hz, 1 H), 4.45 (dd, J = 1.9, 1.9 Hz, 1 H), 4.30 (dd, J = 9.6, 1.9 Hz, 1 H), 3.51 (dd, J = 11.7, 1.9 Hz, 1 H), 3.24 (s, 3 H), 1.57 (s, 3 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.7, 147.6, 143.0, 110.7, 108.9, 102.8, 99.3, 86.9, 79.1, 76.7, 76.5, 49.7, 44.4, 28.3, 25.3, 24.9, 24.1 ppm.

(1*R,5*R**,6*R**,7*R**,8*S**)-6-(2-Furyl)-8-(1-methoxy-1-methylethoxy)-3,3-dimethyl-9-methylene-7-nitro-2,4-dioxabicyclo[3.3.1]nonane (11):** A suspension of $MePPh_3Br$ (3.56 g, 10.03 mmol, 3.5 equiv.) in dry THF (14.2 mL) was treated under argon at –78 °C with *n*BuLi (1.6 M in hexanes, 5.4 mL, 8.59 mmol, 3 equiv.), allowed to reach room temp., stirred for 30 min, and cooled again to –78 °C. A solution of **10** (1.16 g, 2.86 mmol) in dry THF (14.2 mL) was added by cannula, and the mixture was allowed to warm to room temp., stirred for 0.5 h, quenched with H_2O (15.7 mL), and extracted with CH_2Cl_2 (3 × 20 mL). Chromatography (AcOEt/hexane 15%) afforded **11** (1.01 g, 96%) as a light brown solid, R_f = 0.54 (AcOEt/hexane 20%), m.p. 103–105 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34 (d, J = 1.0 Hz, 1 H), 6.36 (d, J = 3.1 Hz, 1 H), 6.32 (dd, J_1 = 3.1, J_2 = 1.0 Hz, 1 H), 5.43–5.19 (m, 3 H), 4.83 (br. s, 1 H), 4.68 (br. s, 1 H), 4.16 (dd, J_1 = 9.6, J_2 = 1.8 Hz, 1 H), 3.45 (dd, J_1 = 11.6, J_2 = 1.8 Hz, 1 H), 3.28 (s, 3 H), 1.53 (s, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.9, 142.2, 141.1, 113.0, 110.6, 108.0, 102.0, 98.6, 88.5, 76.9, 74.7, 73.7, 49.7, 47.5, 30.0, 27.8, 25.1, 24.3 ppm.

(3a*R,5*R**,6*R**,7*R**,7a*S**)-6-(2-Furyl)-2,2-dimethyl-4-methylene-7-nitrohexahydro-1,3-benzodioxol-5-ol (12):** A magnetically stirred solution of **11** (1.94 g, 5.29 mmol) in dry acetone (53 mL) was treated under argon at room temp. first with *p*TsOH·H_2O (101 mg, 0.53 mmol) and, after 4 h, with Et_3N (0.8 mL). Removal of the volatiles (rotary evaporator) followed by chromatography (20% AcOEt/hexane) gave **12** (1.33 g, 85%) as a white solid, R_f = 0.20 (AcOEt/hexane 20%), m.p. 104–108 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37 (s, 1 H), 6.34 (s, 2 H), 5.60 (s, 1 H), 5.57 (s, 1 H), 5.28 (dd, J_1 = 12.4, J_2 = 8.4 Hz, 1 H), 4.77 (d, J = 5.2 Hz, 1 H), 4.67 (dd, J_1 = 8.4, J_2 = 5.2 Hz, 1 H), 4.61 (br. s, 1 H), 3.41 (dd, J_1 = 12.4, J_1 = 1.6 Hz, 1 H), 2.47 (d, J = 4.3 Hz, 1 H), 1.66 (s, 1 H), 1.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.4, 142.6, 139.0, 124.3, 111.3, 110.6, 108.4, 87.4, 78.0, 77.8, 73.3, 44.5, 28.3, 26.0 ppm. LRMS (ESI-TOF): m/z (%) = 318.1 (100) $[M + Na]^+$, 296.1 (17) $[M + H]^+$, 245.1 (93). HRMS (ESI-TOF): calcd. for $C_{14}H_{17}NO_6$ $[M + H]^+$ 296.1134; found 296.1128.

(3a*S,4*S**,5*R**,6*R**,7*R**,7a*S**)-6-(2-Furyl)-2,2,2′,2′-tetramethyl-7-nitrotetrahydro-3a*H*-spiro[1,3-benzodioxole-4,4′-[1,3]dioxolan]-5-ol (14):** *N*-Methylmorpholine *N*-oxide (NMMO, 475 mg, 4.06 mmol, 3 equiv.) and OsO_4 (1 M in H_2O, 54 mL, 0.054 mmol, 0.04 equiv.) were added at room temp. to a magnetically stirred solution of **12** (399 mg, 1.35 mmol) in THF/H_2O (1:1, 27.4 mL). After 18 h, the reaction mixture was treated with a saturated aqueous solution of $Na_2S_2O_3$ (15.7 mL) and, after removal of the THF (rotary evaporator), extracted with AcOEt. The combined organic extracts were dried, and the solvent was removed (rotary evaporator). A solution of the crude diol **13** in acetone (13.5 mL) was treated with 2,2-dimethoxypropane (DMP, 0.24 mL, 1.89 mmol, 1.4 equiv.) and *p*TsOH·H_2O (52 mg, 0.27 mmol, 0.2 equiv.) for 15 min and made basic by addition of Et_3N. Removal of the volatiles and chromatography (AcOEt/hexane 30%) gave **14** (383 mg, 77%) as a white solid, R_f = 0.39 (AcOEt/hexane 20%), m.p. 174–177 °C (Et_2O/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37 (d, J = 1.8 Hz, 1 H), 6.38 (dd, J_1 = 3.3, J_2 = 1.8 Hz, 1 H), 6.28 (d, J = 3.3 Hz, 1 H), 5.08 (dd, J_1 = 12.7, J_2 = 8.5 Hz, 1 H), 4.78 (dd, J_1 = 8.5, J_2 = 4.9 Hz, 1 H), 4.37 (d, J = 9.6 Hz, 1 H), 4.30 (d, J = 9.6 Hz, 1 H), 4.26 (dd, J_1 = 4.9, J_2 = 1.1 Hz, 1 H), 4.01 (ddd, J_1 = 6.6, $J_2 \approx$, $J_3 \approx$ 1.4 Hz, 1 H), 3.85 (dd, J_1 = 12.7, J_2 = 1.8 Hz, 1 H), 2.67 (d, J = 6.6 Hz, 1 H), 1.62 (s, 3 H), 1.47 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.9, 142.7, 111.5, 111.2, 110.6, 108.4, 87.6, 79.2, 78.8, 76.8, 74.5, 69.7, 40.3, 28.2, 26.7, 26.6, 25.9 ppm. LRMS (CI): m/z (%) = 370.1 (64) $[M + H]^+$, 323.1 (68), 312.0 (100), 207.0 (76). HRMS (CI): calcd. for $C_{17}H_{24}NO_8$ $[M + H]^+$ 370.1501292; found 370.1501239.

(3a*S,4*S**,5*R**,6*R**,7*R**,7a*S**)-5-Hydroxy-2,2,2′,2′-tetramethyl-7-nitrotetrahydro-3a*H*-spiro[1,3-benzodioxole-4,4′-[1,3]dioxolane]-6-carboxylic Acid (15):** $NaIO_4$ (5.3 g, 24.96 mmol, 8 equiv.) and $RuCl_3$ (0.312 mmol, 0.1 equiv.) were added to a magnetically stirred solution of **14** (1.15 g, 3.12 mmol) in a solvent mixture of CH_3CN (15.6 mL), CCl_4 (15.6 mL), and H_2O (19.5 mL). After 20 min, silica gel (5 g) was added, and the solvents were removed (rotary evaporator). Column chromatography (AcOEt/hexane 40%, 1% AcOH) gave **15** [560 mg, 52%, R_f = 0.28 (AcOEt/hexane 40%, 1% AcOH), m.p. 198–204 °C (AcOEt/hexane)] as a white solid. ^{1}H NMR (CD_3CN, 300 MHz): δ = 4.94 (dd, J_1 = 12.2, J_2 = 8.7 Hz, 1 H), 4.39 (dd, J_1 = 8.7, J_2 = 5.0 Hz, 1 H), 4.25 (d, J = 9.6 Hz, 1 H), 4.24 (dd, J_1 = 5.0, J_2 = 1.0 Hz, 1 H), 4.18 (dd, J_1 = 2.3, J_2 = 1.0 Hz, 1 H), 4.16 (d, J = 9.6 Hz, 1 H), 3.36 (dd, J_1 = 12.2, J_2 = 2.3 Hz, 1 H), 1.52 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (CD_3CN, 75 MHz): δ = 171.5, 112.2, 111.8, 85.9, 80.5, 80.0, 77.9, 73.1, 69.8, 46.6, 28.2, 27.1, 26.5, 26.0 ppm. LRMS (CI)$^+$ m/z (%) = 348.1 (35) $[M + H]^+$, 290.0 (50), 199.1 (79), 123.0 (100). HRMS (CI): calcd. for $C_{14}H_{22}NO_9$ $[M + H]^+$ 348.129457; found 348.129635.

(3a*S,4*S**,5*R**,6*S**,7*R**,7a*S**)-6-(Hydroxymethyl)-2,2,2′,2′-tetramethyl-7-nitrotetrahydro-3a*H*-spiro[1,3-benzodioxole-4,4′-[1,3]dioxolan]-5-ol (16):** A solution of **15** (260 mg, 0.75 mmol) in dry THF (7.5 mL) was treated under argon at room temp. with BH_3·THF (1 M in THF, 2.99 mL, 2.99 mmol, 4 equiv.), stirred for 14 h, and quenched with H_2O. Removal of the volatiles (rotary evaporator) and chromatography (AcOEt/hexane 40%, 1% AcOH) gave **16** (169.4 mg, 68%) as a white solid, R_f = 0.49 (AcOEt/hexane 40%, 1% AcOH), m.p. 133–135 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.98 (dd, J_1 = 12.5, J_2 = 8.5 Hz, 1 H), 4.79 (dd, J_1 = 8.5, J_2 = 5.0 Hz, 1 H), 4.35 (d, J = 9.5 Hz, 1 H), 4.26 (d, J = 9.5 Hz, 1 H), 4.22 (d, J = 5.0 Hz, 1 H), 4.06 (br. s, 1 H), 3.89 (dd, J_1 = 11.6, J_2 = 3.0 Hz, 1 H), 3.79 (dd, J_1 = 11.6, J_2 = 4.9 Hz, 1 H), 3.18 (br. s, 1 H), 2.53–2.48 (m, 1 H), 1.58 (s, 3 H), 1.44 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 111.3, 111.1, 86.2, 79.3, 78.6, 76.8, 75.0, 69.5, 62.2, 40.4, 28.2, 26.7, 26.6, 25.9 ppm. LRMS (CI): m/z (%) = 334.1 (100) $[M + H]^+$, 317.3 (65), 276.1 (91). HRMS (CI): calcd. for $C_{14}H_{24}NO_8$ $[M + H]^+$ 334.150192; found 334.150459.

(3a*S,4*S**,5*R**,6*S**,7*R**,7a*S**)-6-{[(*tert*-Butyldiphenylsilyl)oxy]-methyl}-2,2,2′,2′-tetramethyl-7-nitrotetrahydro-3a*H*-spiro[1,3-benzodioxole-4,4′-[1,3]dioxolan]-5-ol (17):** Imidazole (757 mg, 2.7 mmol, 10 equiv.) and TBDPSCl (0.29 mL, 1.10 mmol, 4 equiv.) were added under argon at room temp. to a solution of **16** (92 mg, 0.27 mmol) in CH_2Cl_2 (2.75 mL). The reaction mixture was stirred for 20 min, treated with a saturated aqueous solution of $NaHCO_3$ (2.7 mL), and extracted with CH_2Cl_2. Chromatography (AcOEt/hexane 15%) afforded **17** (128 mg, 81%) as a white solid, R_f = 0.57 (AcOEt/hexane 20%), m.p. 44–47 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.7–7.6 (m, 4 H), 7.5–7.4 (m, 6 H), 4.84 (dd, J_1 = 12.5, J_2 = 8.5 Hz, 1 H), 4.71 (dd, J_1 = 8.5, J_2 = 4.9 Hz,

1 H), 4.36 (d, J = 9.5 Hz, 1 H), 4.26 (d, J = 9.5 Hz, 1 H), 4.20 (d, J = 4.9 Hz, 1 H), 4.06 (d, J = 5.7 Hz, 1 H), 3.77 (dd, J_1 = 10.7, J_2 = 6.3 Hz, 1 H), 3.72 (dd, J_1 = 10.7, J_2 = 4.0 Hz, 1 H), 2.93 (d, J = 5.7 Hz, 1 H), 2.57 (m, 1 H), 1.55 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.6 (2 C), 135.4 (2 C), 132.4, 132.2, 130.1, 130.0, 127.9 (2 C), 127.9 (2 C), 111.2, 110.9, 86.7, 79.5, 78.8, 77.1, 73.2, 69.6, 62.3, 41.0, 28.2, 26.8 (3 C), 26.7, 26.6, 25.9, 19.1 ppm. LRSM (ESI-TOF): m/z (%) = 594.2 $[M + Na]^+$ (100), 353.4 (41), 314.6 (55). HRMS (ESI-TOF): calcd. for $C_{30}H_{41}NNaO_8Si$ $[M + Na]^+$ 594.2499; found 594.2494.

(3a*S,4*S**,5*R**,6*S**,7a*R**)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-5-hydroxy-2,2,2′,2′-tetramethyltetrahydro-7*H*-spiro[1,3-benzodioxole-4,4′-[1,3]dioxolan]-7-one (18):** A solution of **17** (141 mg, 0.25 mmol) in toluene (15 mL) was treated at 0 °C under argon with *t*BuOK (45 mg, 0.37 mmol, 1.5 equiv.). After stirring at room temp. for 40 min, the reaction mixture was cooled to –78 °C, and ozone was bubbled through for 45 min. AcOH (177 μL) and Zn (dust, 177 mg) were then added, and the mixture was allowed to warm to room temp., stirred for 0.5 h, treated with a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted (CH_2Cl_2, 3 × 10 mL). Chromatography (AcOEt/hexane 20%) gave **18** (61.3 mg, 45%) as a white solid, R_f = 0.39 (AcOEt/hexane 20%), m.p. 151–152 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75–7.65 (m, 4 H), 7.45–7.35 (m, 6 H), 4.49 (d, J = 5.0 Hz, 1 H), 4.46 (d, J = 9.5 Hz, 1 H), 4.43–4.39 (m, 2 H), 4.32 (d, J = 9.5 Hz, 1 H), 4.11 (dd, J_1 = 10.6, J_2 = 8.4 Hz, 1 H), 4.04 (dd, J_1 = 10.6, J_2 = 4.4 Hz, 1 H), 3.27–3.22 (m, 1 H), 2.66 (d, J = 9.1 Hz, 1 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 206.4, 135.6 (2 C), 135.5 (2 C), 133.3, 133.1, 129.7 (2 C), 127.7 (4 C), 111.3, 111.1, 82.9, 78.9, 78.5, 76.0, 69.9, 58.8, 52.2, 27.1, 26.8 (3 C), 26.7 (2 C), 25.9, 19.2 ppm. LRMS (ESI-TOF): m/z (%) = 563.2 (100) $[M + Na]^+$, 463.2 (77), 405.1706 (39). HRMS (ESI-TOF): calcd. for $C_{30}H_{41}O_7Si$ $[M + H]^+$ 541.2622; found 541.2616.

(3a*S,4*S**,5*R**,6*S**,7a*R**)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-(methoxymethoxy)-2,2,2′,2′-tetramethyldihydro-3a*H*-spiro-[benzo[*d*][1,3]dioxole-4,4′-[1,3]dioxolan]-7(7a*H*)-one (19):** $CH_2(OMe)_2$ (59 μL, 0.68 mmol, 20 equiv.) and P_2O_5 (9.6 mg, 0.068 mmol, 2 equiv.). were added under argon at room temp. to a solution of **18** (18 mg, 0.034 mmol) in dry CH_2Cl_2, and the mixture was stirred for 1.5 h. After addition of more P_2O_5 (43 mg) and stirring (3 h), a saturated aqueous solution of $NaHCO_3$ (1 mL) was added. Extraction (CH_2Cl_2, 3 × 2 mL) and chromatography (AcOEt/hexane 15%) gave **19** (16.3 mg, 82%) as a white solid [R_f = 0.5 (AcOEt/hexane 20%)]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.7–7.6 (m, 4 H), 7.4–7.3 (m, 6 H), 4.62 (d, J = 6.7 Hz, 1 H), 4.54 (d, J = 6.7 Hz, 1 H), 4.44 (dd, J_1 = 6.0, J_2 = 1.9 Hz, 1 H), 4.43 (d, J = 9.6 Hz, 1 H), 4.40 (d, J = 6.0 Hz, 1 H), 4.37 (dd, J_1 = 2.5, J_2 = 2.3 Hz, 1 H), 4.35 (d, J = 9.6 Hz, 1 H), 4.01 (dd, J_1 = 11.0, J_2 = 4.9 Hz, 1 H), 3.93 (dd, J_1 = 11.0, J_2 = 10.2 Hz, 1 H), 3.30 (s, 3 H), 3.27 (ddd, J_1 = 10.2, J_2 = 4.9, J_3 = 2.5 Hz, 1 H), 1.51 (s, 3 H), 1.49 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.09, 135.54 (4 C), 133.21 (2 C), 129.80, 129.78, 127.75 (2 C), 127.70 (2 C), 111.01, 110.80, 98.67, 82.83, 82.27, 79.24, 78.57, 69.83, 58.32, 55.73, 51.51, 26.92, 26.85 (3 C), 26.80, 26.75, 26.23, 19.19 ppm. LRMS (ESI-TOF): m/z (%) = 607.3 (100) $[M + Na]^+$, 364.3 (12) 475.3 (6). HRMS (ESI-TOF): calcd. for $C_{32}H_{44}NaO_8Si$ $[M + Na]^+$ 607.2703; found 607.2698.

CCDC-784303 (**8**) and CCDC-784304 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Large-scale preparation of **2** and **3**; timetables for the preparation of IBX, **3**, **5**, and **7**; analytical and spectroscopic data (^{1}H NMR, ^{13}C NMR, and DEPT spectra) for **2**, **3**, **7**, **8**, **10**–**12**, and **14**–**19** and GC–MS (CI) monitoring of the formation of the enamine **6**.

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[1] A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477–1489.
[2] Tetrodotoxin, tarichatoxin, and chiriquitoxin: historical perspectives, in F. A. Fuhrman, *Ann. N. Y. Acad. Sci.* **1986**, *479*, 1–14.
[3] a) *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel*: C. Y. Kao, S. R. Levinson, *Ann. N. Y. Acad. Sci.* **1986**, *479*; b) D. B. Tikhonov, B. S. Zhorov, *Biophys. J.* **2005**, *88*, 184–197; c) S. L. Geffeney, E. Fujimoto, E. D. Brodie, E. D. Brodie , P. C. Ruben, *Nature* **2005**, *434*, 759–763.
[4] M. Noda, S. Shimizu, T. Tanabe, T. Takai, T. Kayano, T. Ikeda, H. Takahashi, H. Nakayama, Y. Kanaoka, N. Minamino, K. Kangawa, H. Matsuo, M. A. Raftery, T. Hirose, S. Inayama, H. Hayashida, T. Miyata, S. Numa, *Nature* **1984**, *312*, 121–127.
[5] F. Hucho, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 39–50.
[6] For the period 2005–2009, SciFinder Scholar retrieves around 700 references per year for tetrodotoxin in the Chemical Abstracts database, mostly relating to neurological and pharmacological studies.
[7] The chemistry of tetrodotoxin, in: H. S. Mosher, *Ann. N. Y. Acad. Sci.* **1986**, *479*, 32–43.
[8] Tetrodotoxin is the main lead compound in WexPharmaceuticals' drug development program: http://www.wexpharma.com/.
[9] For recent papers on the therapeutic potential of sodium channel blockers, see: a) R. J. French, H. Terlau, *Curr. Med. Chem.* **2004**, *11*, 3053–3064; b) J. N. Wood, J. Boorman, *Curr. Top. Med. Chem.* **2005**, *5*, 529–537; c) I. Tarnawa, H. Bolcskei, P. Kocsis, *Recent Pat. CNS Drug Discov.* **2007**, *2*, 57–78; d) W. E. Childers, A. M. Gilbert, J. D. Kennedy, G. T. Whiteside, *Expert Opin. Ther. Pat.* **2008**, *18*, 1027–1067.
[10] The structural determination of tetrodotoxin was reported at the 3rd IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 13, **1964** by the groups led by Tsuda, Hirata, Woodward, and Mosher; a) K. Tsuda, O. Amakasu, S. Ikuma, M. Kawamura, C. Tamura, R. Tachikawa, K. Sakai, *Chem. Pharm. Bull.* **1964**, *12*, 1357; b) T. Goto, Y. Kishi, S. Takahashi, Y. Hirata, *Tetrahedron* **1965**, *21*, 2059–2088; c) R. B. Woodward, *Pure Appl. Chem.* **1964**, *9*, 49; d) R. B. Woodward, J. Z. Gougoutas, *J. Am. Chem. Soc.* **1964**, *86*, 5030; e) H. S. Mosher, H. G. Fischer, F. A. Fuhrman, H. D. Buchwald, *Science* **1964**, *144*, 1100–1111.
[11] a) Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9217–9219; b) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, *94*, 9219–9221.
[12] More recently, the group led by Sato reported a stereocontrolled synthesis of racemic tetrodotoxin from myo-inositol: K.-i. Sato, S. Akai, N. Sugita, T. Ohsawa, T. Kogure, H. Shoji, J. Yoshimura, *J. Org. Chem.* **2005**, *70*, 7496–7504.
[13] a) N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798–8805; b) A. Hinman, J. Du Bois, *J. Am. Chem. Soc.*

2003, *125*, 11510–11511; c) T. Nishikawa, D. Urabe, M. Isobe, *Angew. Chem. Int. Ed.* **2004**, *43*, 4782–4785; d) P. Noheda, "Synthesis of tetrodotoxin, its analogues and intermediates thereof" EP 1785427, **2007**; e) K.-i. Sato, S. Akai, H. Shoji, N. Sugita, S. Yoshida, Y. Nagai, K. Suzuki, Y. Nakamura, Y. Kajihara, M. Funabashi, J. Yoshimura, *J. Org. Chem.* **2008**, *73*, 1234–1242; f) S. Akai, H. Seki, N. Sugita, T. Kogure, N. Nishizawa, K. Suzuki, Y. Nakamura, Y. Kajihara, J. Yoshimura, K. Sato, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 279.

[14] For other synthetic efforts directed towards tetrodotoxin, see the following articles and the references cited therein: a) J. F. W. Keana, J. S. Bland, P. J. Boyle, M. Erion, R. Hartling, J. R. Husman, R. B. Roman, G. Ferguson, M. Parvez, *J. Org. Chem.* **1983**, *48*, 3627–3631; b) R. J. Nachman, M. Honel, T. M. Williams, R. C. Halaska, H. S. Mosher, *J. Org. Chem.* **1986**, *51*, 4802–4806; c) C. S. Burgey, R. Vollerthun, B. Fraser-Reid, *J. Org. Chem.* **1996**, *61*, 1609–1618; d) T. Itoh, M. Watanabe, T. Fukuyama, *Synlett* **2002**, 1323–1325; e) T. Umezawa, T. Hayashi, H. Sakai, H. Teramoto, T. Yoshikawa, M. Izumida, Y. Tamatani, T. Hirose, Y. Ohfune, T. Shinada, *Org. Lett.* **2006**, *8*, 4971; f) D. F. Taber, P. H. Storck, *J. Org. Chem.* **2003**, *68*, 7768–7771; g) L. Ozores, F. Cagide, R. Alonso, *Synlett* **2004**, 2746–2750; h) B. A. Mendelsohn, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 4736.

[15] a) In his highlight article "Syntheses of Tetrodotoxin", U. Koert, *Angew. Chem. Int. Ed.* **2004**, *43*, 5572–5576, the author concludes: "All three syntheses (those of Isobe and Du Bois, ref.[13a–13c] above) are long (>25 steps) and follow a linear strategy. The hexasubstituted cyclohexane intermediate makes a convergent strategy, which may reduce the number of steps to less than 20, very difficult but not impossible. Because of its structural complexity and functional-group density, tetrodotoxin will remain a prime synthetic target."; b) number of steps (and overall yields in parentheses) for the total synthesis of TTX reported in refs.[11,12,13a–13c,13e], are: 29 (0.66%), 40 (0.14%), 69 (0.17%), 32 (0.49%), 62 (1%) and 34 (0.38%), respectively.

[16] J. C. Ortiz, L. Ozores, F. Cagide-Fagin, R. Alonso, *Chem. Commun.* **2006**, 4239–4241.

[17] P. Martínez-Bescos, F. Cagide-Fagin, L. F. Roa, J. C. Ortiz-Lara, K. Kierus, L. Ozores-Viturro, M. Fernández-González, R. Alonso, *J. Org. Chem.* **2008**, *73*, 3745–3753.

[18] Preparation of the nitroenal **3** involves final oxidation with IBX; while caution should always be exercised when dealing with this reagent (see ref.[19]), we prepared it more than 15 times in batches of 65 g without a single incident according to the procedure reported in: D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.

[19] **Caution**! IBX is explosive under impact or heating above 200 °C: J. B. Plumb, D. J. Harper, *Chem. Eng. News* **1990**, *68*, 3; see also comments in: G. Tojo, M. Fernández, in *Basic Reactions in Organic Synthesis Oxidation of Alcohols to Aldehydes and Ketones*, Springer, New York, **2006**, chapter 3, pp. 203 and 183, respectively, and references therein.

[20] For experimental procedures to prepare 2,2-dimethyl-1,3-dioxan-5-one (**5**), see: a) D. Enders, M. Voith, S. J. Ince, *Synthesis* **2002**, 1775–1779; b) D. C. Forbes, D. G. Ene, M. P. Doyle, *Synthesis* **1998**, 879–882, and references cited therein; reported yields for the two-step procedure in refs.[20a,20b] are 58% (on the 25 g scale) and 73% (10 g scale), respectively.

[21] A timetable for the whole process – the preparations of IBX, the nitroenal **3**, the dioxanone **5**, and the protected nitrocyclitol **7** – is included in the Supporting Information

[22] Detailed experimental procedures for the gram-scale preparation of **7** and its precursor **3** are described in the Experimental Section and the Supporting Information, respectively.

[23] Although we found no precedent for the deformylation of α-nitro aldehydes, other α-nitro carbonyl derivatives, in particular α-nitro ketones, are known to undergo C(O)–$C_\alpha(NO_2)$ cleavage at their carbonyl groups as a result of the addition of a range of agents (water, alcohols, amines, thiols, etc.); see for example: R. H. Fischer, H. M. Weitz, *Synthesis* **1980**, 261–282.

[24] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.

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