Synthetic Approach to Tetrodotoxin

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Abstract: A novel and stereoselective approach to tetrodotoxin is described. The tricyclic compound having several key functional groups on the cyclohexane ring was synthesized from *p*-anisaldehyde with control of the four chiral centers. Iodoaminocyclization, 1,3-dipolar cycloaddition, and Baeyer–Villiger oxidation are the key steps of our approach.

Key words: tetrodotoxin, stereoselective, iodoaminocyclization reaction, intramolecular 1,3-dipolar cycloaddition, isoxazoline

Tetrodotoxin (**1**),[1] found mostly in the livers and ovaries of puffer fish, is one of the most well-known and most toxic marine natural products having low molecular weights (Figure). Because of its biological activities as well as its unique and complex structure,[2] tetrodotoxin has been one of the most attractive and challenging synthetic targets in the field of synthetic organic chemistry.[3] In spite of many efforts, only one total synthesis of tetrodotoxin has been reported by Kishi and co-workers in 1972.[4] The complex structure of tetrodotoxin could be simplified as shown in the Figure by removal of the ortho ester and guanidine moieties. In this communication, we report a new synthetic route to the tricyclic compound **2** having several functional groups of the core skeleton of tetrodotoxin on the cyclohexane ring with control of the four contiguous stereocenters. Our approach features iodoaminocyclization reaction of imidodicarbonate, 1,3-dipolar cycloaddition, and Baeyer–Villiger oxidation.

The imidodicarbonate **6** was prepared from *p*-anisaldehyde (**3**) in six steps (Scheme 1). Addition of allylmagnesium bromide to **3** followed by ozonolysis and subsequent reduction of the resulting aldehyde afforded the 1,3-diol **4**. Birch reduction of **4** gave the 1,4-diene, which was converted to the dimethylacetal **5** upon treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol. After selective protection of the primary alcohol, the imidodicarbonate **6** was easily synthesized by the reaction with benzyloxycarbonyl isocyanate which in turn was prepared in situ from benzylcarbamate, triphosgen, and pyridine. This method was more practical than the reported one[5] because it was not necessary to isolate the very reactive and moisture sensitive alkoxycarbonyl isocyanates. With the precursor of iodoaminocyclization reaction in hand, we attempted to construct the bicyclic system according to Taguchi's protocol.[6] Upon successive treatment with 1.8 equivalents of LiAl(*t*-BuO)$_4$ and 5.0 equivalents of iodine, iodoaminocyclization reaction proceeded successfully to give the bicyclic oxazolidinone **7** with modest diastereoselectivity (ds = 3:1).[7] To the best of our knowledge, diastereoselective construction of a quaternary carbon adjacent to nitrogen by this reaction has not been reported to date.[8]

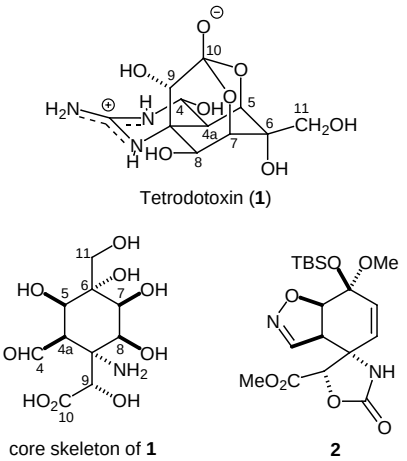
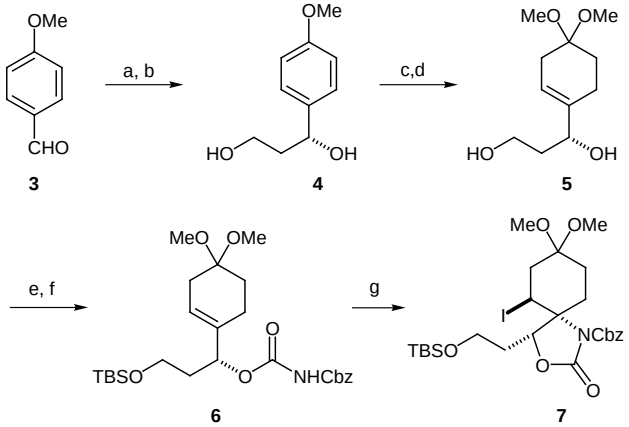


Figure Structures of tetrodotoxin (**1**), its core skeleton, and the tricyclic compound **2** (described in this communication).



Scheme 1 *Reagents and Conditions:* (a) Allylmagnesium bromide, ether, 0 °C; (b) O_3, CH_2Cl_2–MeOH (1:1), –78 °C; $NaBH_4$, 0 °C; (c) Li, EtOH, THF, liquid NH_3, reflux, 5 min; (d) cat. PPTS, MeOH, r.t., 85% (4 steps); (e) TBSCl, imidazole, CH_2Cl_2, 0 °C. 89%; (f) triphosgene, benzyl carbamate, pyridine, CH_2Cl_2, 0 °C, 97%; (g) LiAl(*t*-BuO)$_4$, THF; I_2, r.t.

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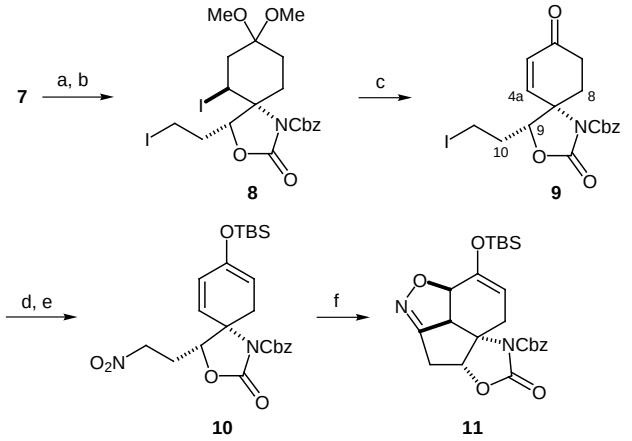
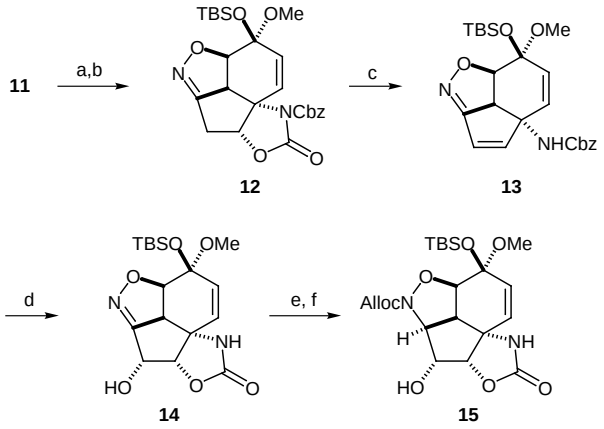
In order to prepare a precursor of the ensuing intramolecular 1,3-dipolar cycloaddition, **7** was converted to the nitroalkane **10** in 5 steps (Scheme 2). After deprotection of the silyl group, the resulting alcohol was converted to the iodide **8**. Hydrolysis of the dimethylacetal of **8** with 80% aqueous acetic acid at 100 °C caused concomitant dehydroiodination to yield the enone **9** quantitatively. After formation of the silyl enol ether, **10** was synthesized by substitution reaction with sodium nitrite in DMF. Upon treatment of **10** with di-*tert*-butyl dicarbonate and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in acetonitrile,[9] smooth formation of the nitrile oxide and the subsequent intramolecular 1,3-dipolar cycloaddition with the olefin occurred to give the isoxazoline **11** as a single diastereomer in good yield.



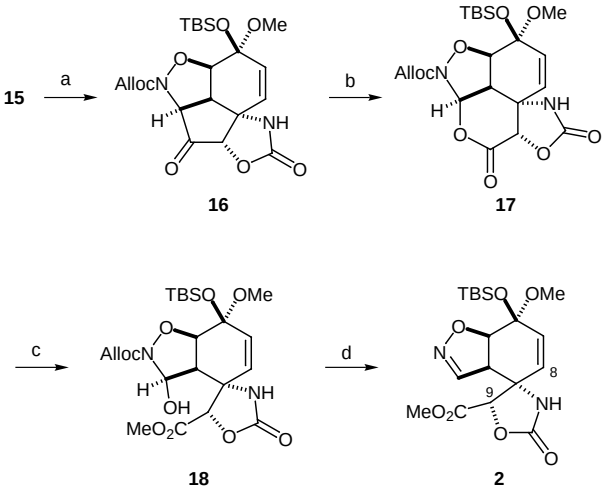
Scheme 2 *Reagents and Conditions:* (a) TBAF, THF, r.t.; (b) PPh_3, I_2, imidazole, benzene, r.t., 54% (3 steps); (c) 80% aq HOAc, 100 °C, quant.; (d) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 89%; (e) $NaNO_2$, DMF, 66%; (f) Boc_2O, cat. DMAP, CH_3CN, 90%.

Having synthesized the tetracyclic compound **11** stereoselectively, we then investigated the oxidation of the cyclohexane and cyclopentane rings (Scheme 3). Introduction of the double bond into the cyclohexane ring was performed by usual procedures. Phenylselenylation of **11** in CH_2Cl_2 and methanol did not afford the expected ketone but instead gave the mixed acetal. After *m*-CPBA oxidation of the selenide, heating the reaction mixture at refluxing temperature caused selenoxide elimination to furnish the cyclohexene **12** in a quantitative yield. Treatment of **12** with DBU caused elimination of carbon dioxide to give the olefin **13**. Dihydroxylation[10] of **13** proceeded selectively at the olefin on the cyclopentene ring from the convex face of the tricyclic system to give a diol, which was converted to the oxazolidinone **14** after reductive and mild basic work-up with saturated Na_2SO_3.[11] Formation of the oxazolidinone allowed the differentiation of the two hydroxy groups. Reduction of the isoxazoline **14** with sodium borohydride followed by selective N-protection of the isoxazolidine with an Alloc group afforded **15**.



Scheme 3 *Reagents and Conditions:* (a) PhSeCl, pyridine, CH_2Cl_2–MeOH, 0 °C, 79%; (b) *m*-CPBA, dichloroethane; $NaHCO_3$, reflux, quant.; (c) DBU, THF, r.t., quant.; (d) cat. OsO_4, NMO, acetone–H_2O–*t*-BuOH, r.t.; sat. Na_2SO_3; (e) $NaBH_4$, MeOH, r.t., 89% (2 steps); (f) Alloc-Cl, sat. $NaHCO_3$–CH_2Cl_2, r.t., 85%.

The alcohol **15** was oxidized to the ketone **16** with Dess–Martin periodinane[12] (Scheme 4). The regioselective Baeyer–Villiger oxidation occurred upon treatment of **16** with *m*-CPBA in the presence of solid sodium bicarbonate to furnish the 6-membered lactone **17**. This lactone was cleaved easily by methanolysis to give the hemiaminal **18**. Palladium-mediated deprotection of the Alloc group of **18** led to further dehydration of the hemiaminal to afford the isoxazoline **2**.[13]



Scheme 4 *Reagents and Conditions:* (a) Dess–Martin periodinane, CH_2Cl_2, r.t.; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t.; (c) K_2CO_3, MeOH, r.t.; (d) cat. $Pd(PPh_3)_4$, pyrrolidine, CH_3CN, r.t., 42% (4 steps).

In conclusion, we have successfully synthesized the tricyclic compound **2** having several key functional groups of tetrodotoxin (**1**) on the cyclohexane ring with control of the four chiral centers. In addition, **2** possesses other functional groups that could potentially provide access to tetrodotoxin. Further elaboration toward the synthesis of tetrodotoxin is currently underway in our laboratory.

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(13) It is known that C-9 position of tetrodotoxin sometimes epimerizes. We confirmed that epimerization at C-9 position of **2** did not occur because NOE between C-8 and C-9 was observed.