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Toward the total synthesis of tetrodotoxin: stereoselective construction of the 7-oxanorbornane intermediate

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ABSTRACT

The stereoselective synthesis of 7-oxanorbornane regarding as a key synthetic intermediate of tetrodotoxin (TTX) is reported. The bicyclo ring bearing various functional groups was successfully elaborated by a furan Diels–Alder (DA) reaction. The stereoselective installation of a quaternary amino carbon center to the DA product was achieved with the Tsuji–Trost allylation. The stereochemistry was unambiguously confirmed with X-ray.

Tetrodotoxin (TTX) (**1**) was originally isolated from the puffer fish, *Spheroides rubripes*, and is responsible for its toxicity.[1,2] TTX is a highly functionalized zwitterion with an *ortho* acid and a cyclic guanidine and aminal. The structure of TTX was independently elucidated by Hirata-Goto, Tsuda, and Woodward in 1964[3] and the absolute stereochemistry was determined using X-ray by Nitta and co-workers in 1970.[4]

TTX (**1**) specifically inhibits voltage-dependent Na^+ channels and has been widely used in neurophysiology and neuroscience.[2] Significant efforts have been devoted to the total synthesis of **1** and its congeners (Fig. 1).[5–7] Since the first total synthesis of racemic **1** was reported by Kishi and Goto in 1972,[8] several have been reported by Isobe and Nishikawa,[9] Du Bois,[10] and Sato.[11] Recently, Nishikawa and Adachi reported the synthesis of one of the highly oxygenated TTX congeners, chiriquitoxin.[12] In 2006, we reported the first total synthesis of 5,6,11-trideoxytetrodotoxin.[13] Our group has been developing a synthetic route to TTX (**1**) and its congeners using a Diels–Alder (DA) reaction (Scheme 1). In this Letter, we report the stereoselective construction of 7-oxanorbornane regarding as a key intermediate **3** in 9 steps. TTX (**1**) can be envisaged as having originated from **2**, which could be accessed through the ring opening of **3**. Compound **3** would be provided by a stereoselective allylation of 7-oxanorbornane **4** from the sterically less hindered *exo*-face. Nitro compound **4** could originate from **5**[14] and **6** via an intermolecular DA reaction. The regio- and stereoselectivities could be determined by the preferential orbital interactions of **5** and **6**.[15]

Furan **5** was prepared from **7** using Tanino's procedure (Scheme 2).[16] To the best of our knowledge, the reaction of nitroolefin **6** with **5** using a DA reaction has not yet been reported. As expected, this proceeded smoothly with high regio- and stereoselectivity [(1*R**, 2*R**, 2*R**, 3*R**)-**4**: (1*R**, 2*S**, 3*S**, and 3*R**)-isomer: others = 20:4:1]. Unstable silylenol ether **8** was subsequently treated with TFA in situ to give **4** in 85% yield. The relative structure of **4** was tentatively assigned (2*R** and 3*R**) by NMR analysis of **4** and X-ray analysis of the advanced synthetic intermediate **19** as described in Scheme 6.

Construction of the quaternary amino carbon center on the bicyclo[2.2.1] system is a challenging task and only a few examples have been reported in related systems.[17] A model study was initially carried out with **9**, which was prepared from **6** and a furan in four steps using a DA reaction (see Supporting information (SI)). Various electrophiles and bases were screened and most of the reactions gave no product (Scheme 3).

Recently, Tunge and Grenning reported the intramolecular allylation of allyl nitroacetates with a decarboxylative Tsuji–Trost reaction.[18] Inspired by this, we attempted to apply this to compound **9** (Table 1). Treatment of **9** with allyl acetate in the presence of a Pd catalyst and NaOMe in MeOH at 50 °C afforded allylated product **10** in 63% yield as a single diastereomer.[19] The reaction conditions were then optimized and treatment with 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % PPh_3, DBU, or MeONa (2.5 equiv), and allyl acetate (2.5 equiv) in DMF at 80 °C for 1 h (entries 7 and 8) allowed for high conversion efficiency. Under the condition in entry 8, the desired product was isolated in 84% yield. In the experiments giving **10** in lower yields (entries 1–6, 9, and 10),

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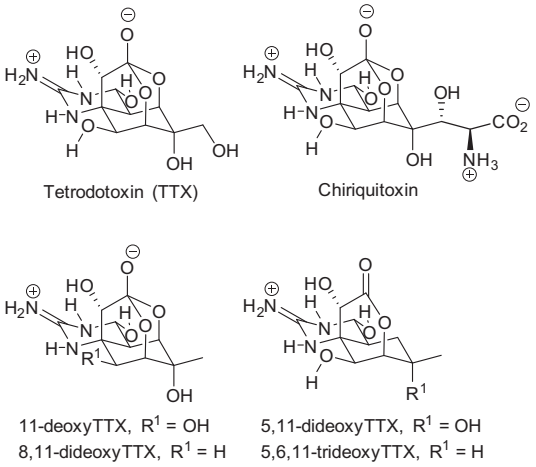
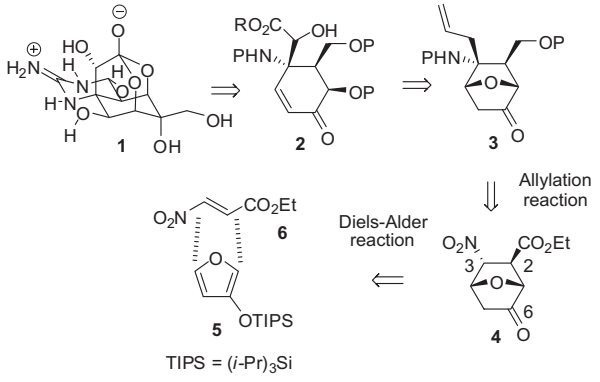
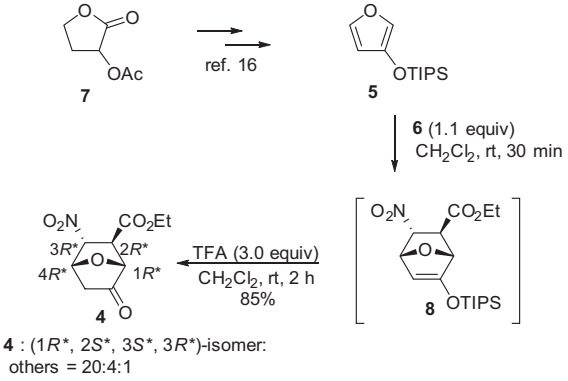


Figure 1. Structure of TTX and its congeners.



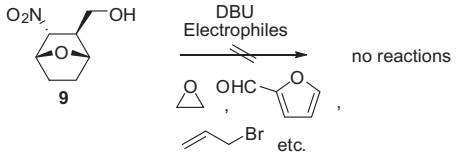
Scheme 1. Retrosynthetic analysis of TTX via intermediate **3**.



Scheme 2. Diels–Alder reaction of **5** and nitro-olefin **6**.

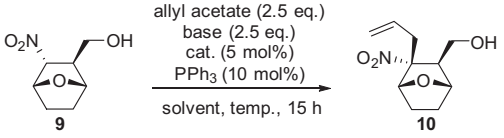
recovery of the starting material **9** was observed. *O*-allylation reactions did not compete under the reaction conditions. The relative stereochemistry of **10** was determined by NOE experiments on the cyclic hemiacetal **11**, which was derived from **10** by ozonolysis (Scheme 4).

The optimum reaction conditions were applied to the synthesis of advanced intermediate **19** (Schemes 5 and 6). This began with the treatment of **4** with DIBAL in CH_2Cl_2, followed by chemoselective protection of the resultant primary alcohol **12**[20,21] to give tert-butyldimethylsilyl (TBS) ether **13**. The stereochemistry of the



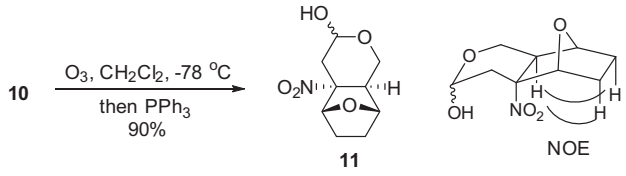
Scheme 3. Model study for the construction of the quaternary carbon center.

Table 1
Optimization of the Tsuji–Trost reaction

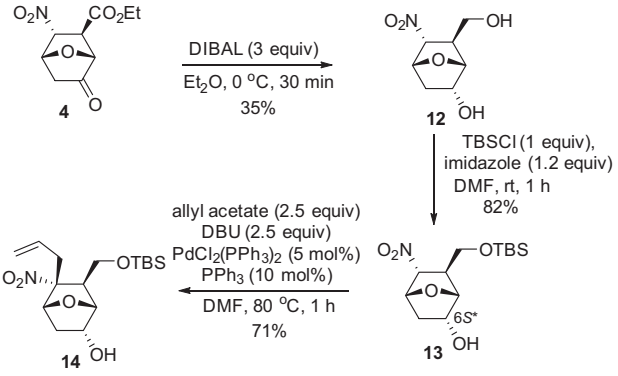


Entry	Cat.	Solvent	Base	Temp. (°C)	Conversion[a] (%)
1	$Pd(PPh_3)_2Cl_2$	MeOH	CH_3ONa	50	63
2	$Pd(o\text{-tolyl-}PPh_3)_2Cl_2$	MeOH	CH_3ONa	50	16
3	$Pd(OAc)_2$	MeOH	CH_3ONa	50	37
4	$Pd_2(dba)_3$	MeOH	CH_3ONa	50	25
5	$Pd(PPh_3)_2Cl_2$	THF	CH_3ONa	50	5
6	$Pd(PPh_3)_2Cl_2$	DMF	CH_3ONa	50	51
7	$Pd(PPh_3)_2Cl_2$	DMF	CH_3ONa	80	100
8[b]	$Pd(PPh_3)_2Cl_2$	DMF	DBU	80	100
9	$Pd(PPh_3)_2Cl_2$	EtOH	CH_3ONa	80	78
10	$Pd(PPh_3)_2Cl_2$	Toluene	CH_3ONa	120	50

[a] Determined by ^1H NMR of the crude mixture.
[b] Isolated yield (84%).



Scheme 4. Determination of the relative stereochemistry.



Scheme 5. Synthesis of intermediate **14**.

secondary hydroxyl group at C6 of **13** was putatively assigned to be 6S* by ^1H NMR analysis (see Experimental section in Supplementary material). As expected, **13** underwent the Tsuji–Trost allylation under the established conditions to give **14** as a single diastereomer in 71% yield.