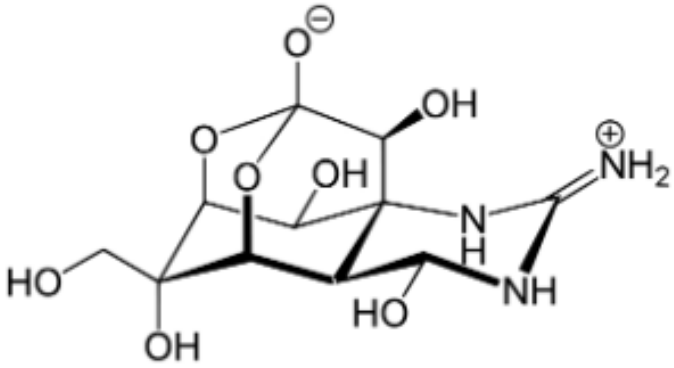
Total Synthesis of (−)-Tetrodotoxin and 11-norTTX-6(*R*)-ol

*Tomoaki Maehara, Keisuke Motoyama, Tatsuya Toma, Satoshi Yokoshima, and Tohru Fukuyama**



Chenjingrong
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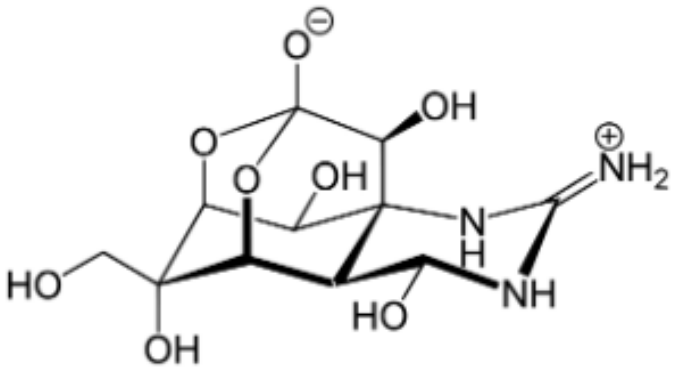
Angew. Chem. Int. Ed. 2017, 56, 1549 – 1552

Tetrodotoxin (TTX)



aminoperhydroquinazoline
(氨基全氢喹唑啉)
$C_{11}H_{17}O_8N_3$

LD_{50} = 334 ug/kg

The chemical structure was revealed by Tsuda Woodward in 1964

The structure was confirmed by X-ray crystallography in 1970.

Yoshito Kishi (Nagoya University), reported the first total synthesis of D,L-tetrodotoxin in 1972.

M. Isobe and J. Du Bois et al. at Stanford University,U.S.,reported the asymmetric total synthesis of tetrodotoxin in 2003.

The two 2003 syntheses used very different strategies, with Isobe's route based on a Diels-Alder approach and Du Bois's work using C-H bond activation.

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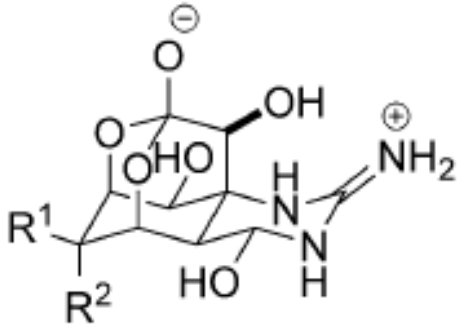
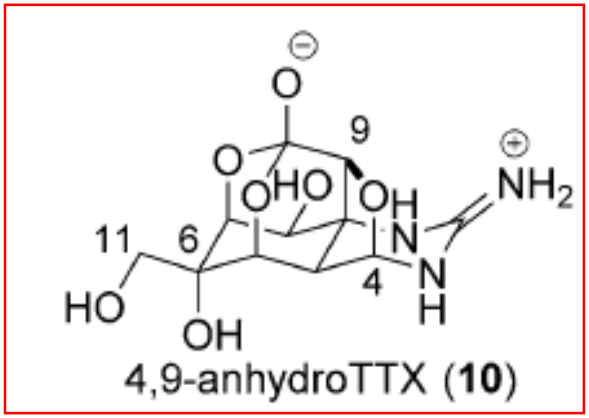
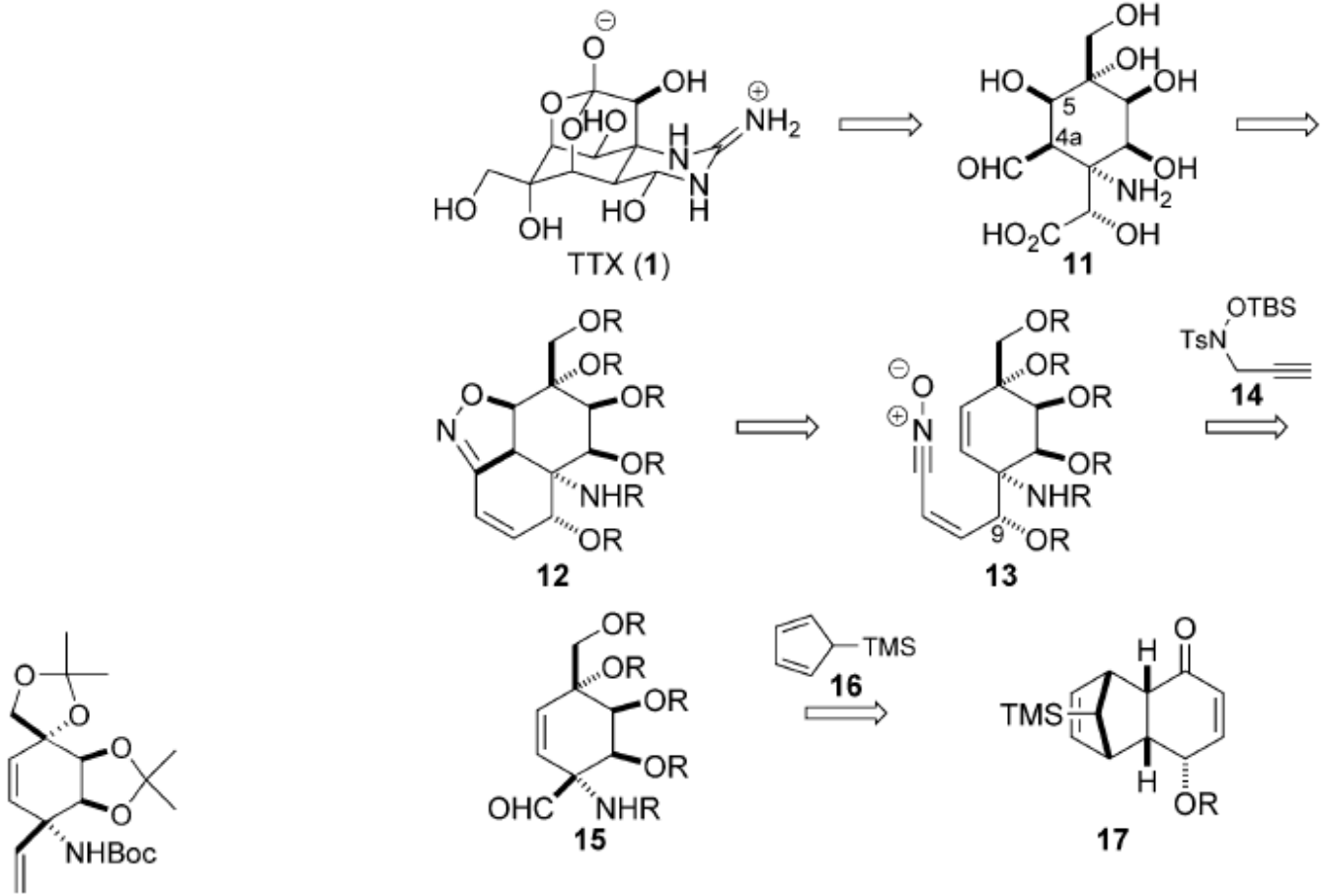


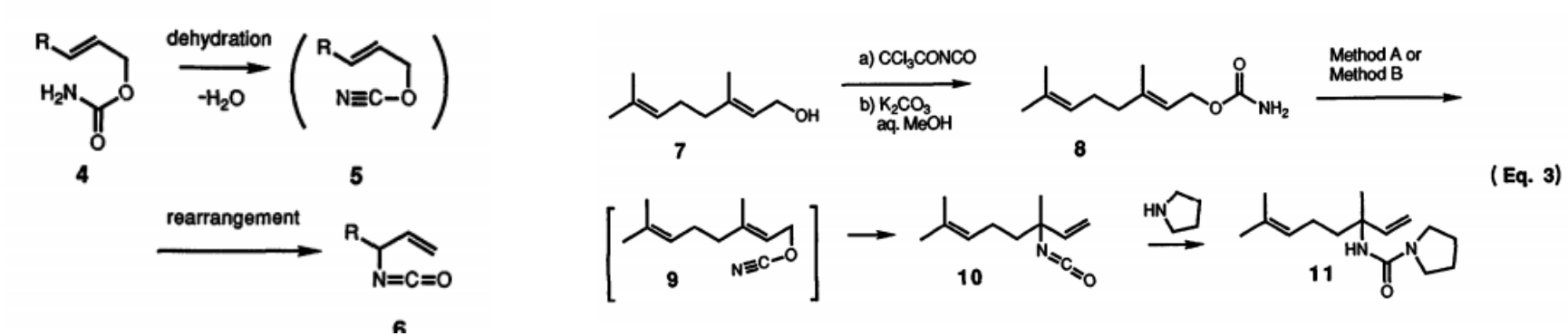


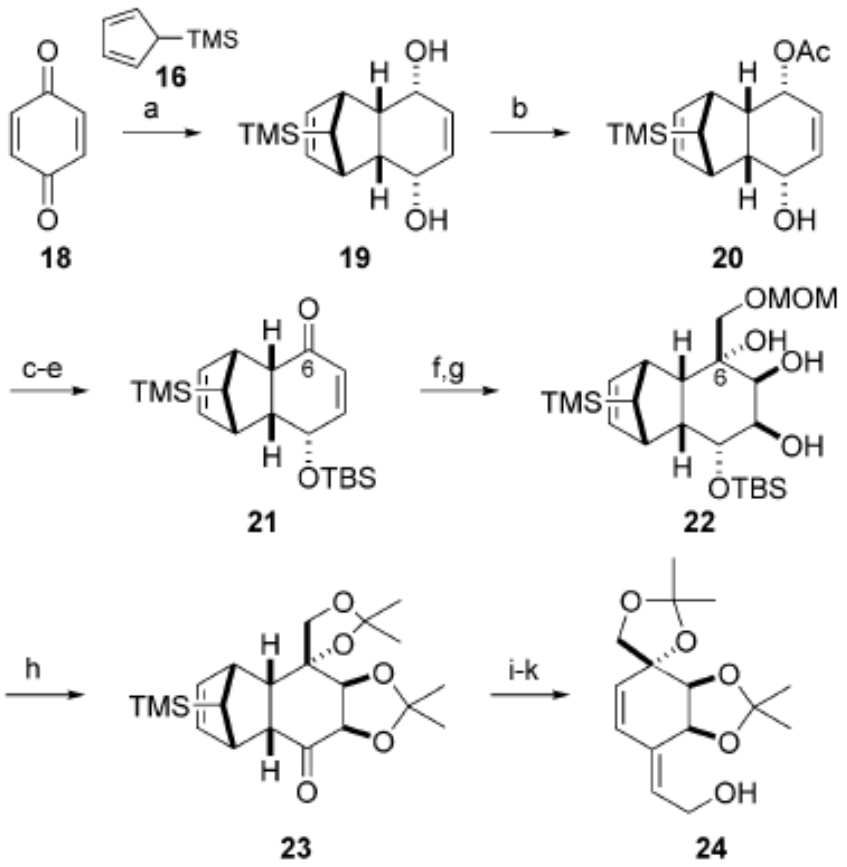
	R^1	R^2
TTX (**1**)	CH_2OH	OH
6-*epi*TTX (**2**)	OH	CH_2OH
11-deoxyTTX (**3**)	CH_3	OH
11-oxoTTX (**4**)	$CH(OH)_2$	OH
TTX-11-carboxylic acid (**5**)	CO_2H	OH
11-norTTX-6,6-diol (**6**)	OH	OH
11-norTTX-6(*R*)-ol (**7**)	OH	H
11-norTTX-6(*S*)-ol (**8**)	H	OH
chiriquitoxin (**9**)	$CH(OH)CH(NH_3^+)COO^-$ (R) (S)	OH

Figure 1. The structure of TTX and its analogues.

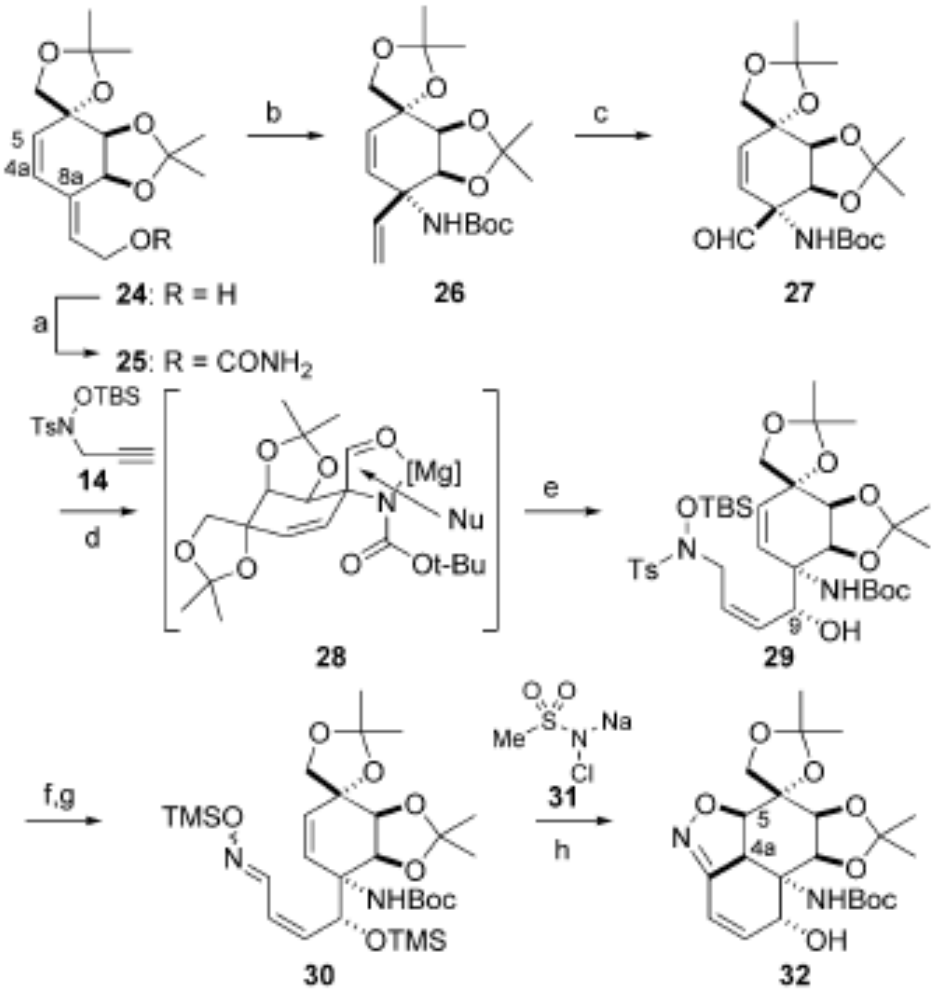


Scheme 1. Retrosynthetic analysis of TTX.

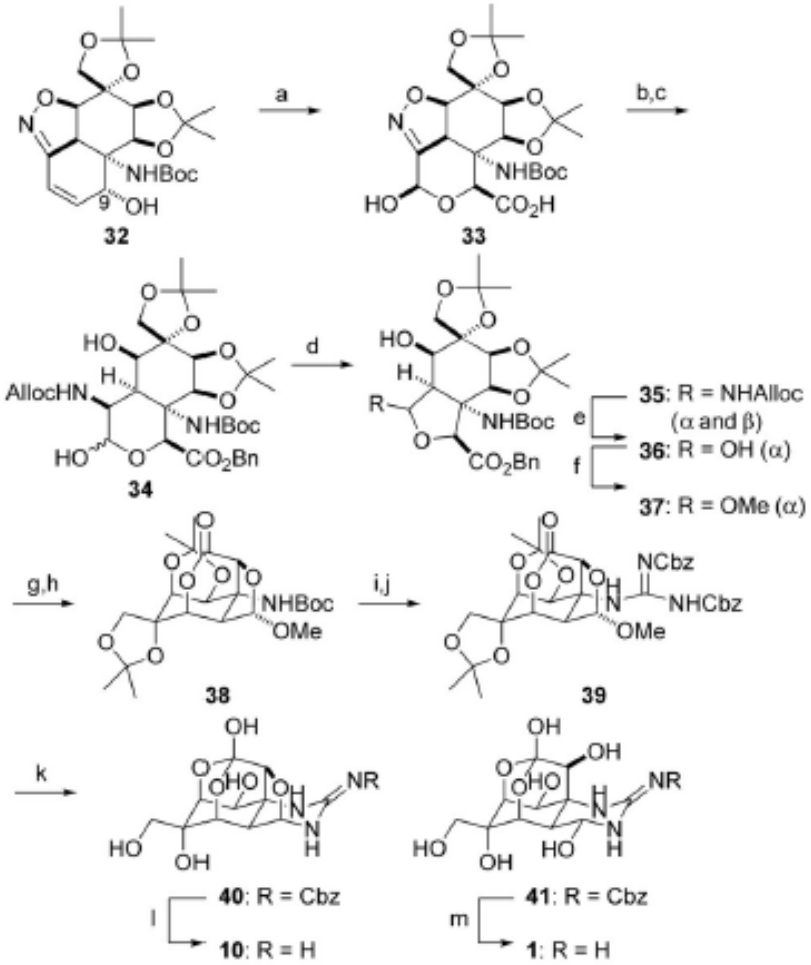




Scheme 2. Stereocontrol at C-6, C-7, and C-8. a) 5-TMS-cyclopentadiene (**16**), CH_2Cl_2, MeOH, RT; $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, 0 °C, 62%; b) isopropenyl acetate, lipase PS IM Amano, Et_3N, RT, 89%, >99% *ee*; c) TBSCl, imidazole, DMF, RT; d) K_2CO_3, MeOH, RT, quant. (2 steps); e) PDC, Celite, DMF, 0 °C; f) *n*-Bu_3SnCH_2OMOM, *n*-BuLi, THF, −98 °C, 73% (2 steps); g) OsO_4, NMO, quinuclidine·HCl, acetone, H_2O, reflux, 90%; h) *p*-TsOH·H_2O, $CuSO_4$, acetone, reflux; Jones' reagent, 0 °C; i) $TMSCH_2CO_2Et$, LDA, THF, −78 to 0 °C; j) *o*-dichlorobenzene, 160 °C; k) DIBAL, toluene, −78 to 0 °C, 38% (4 steps).

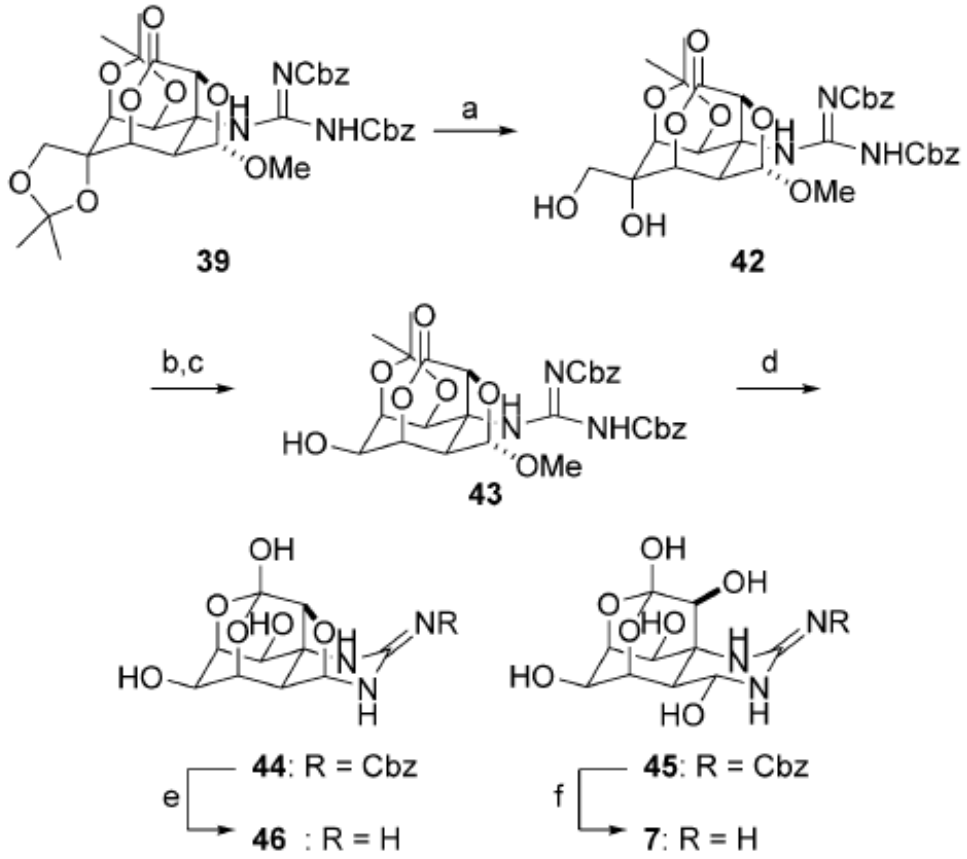


Scheme 3. Intramolecular 1,3-dipolar cycloaddition. a) $Cl_3CC(O)NCO$, CH_2Cl_2, RT; Et_3N, MeOH, RT, 98%; b) TFAA, *i*-Pr_2NEt, CH_2Cl_2, −78°C to RT; LiO*t*-Bu, −78 to 0°C, 79%; c) OsO_4, NMO, acetone, RT; $Pb(OAc)_4$, RT, 75%; d) **14**, EtMgBr, THF, 0°C, 88%; e) H_2, Pd/C, quinoline, EtOH, EtOAc, RT; f) CsF, MeCN, 60°C; g) TMSCl, imidazole, DMF, RT; h) **31**, AcOH, EtOH, RT; aq. HCl, RT, 68% (4 steps).

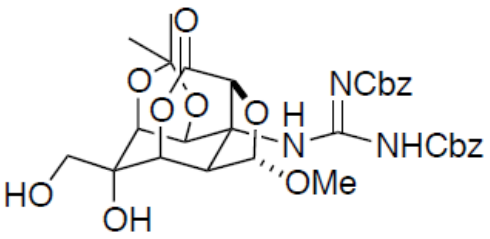


32 33 34 38 39

Scheme 4. Total synthesis of TTX. a) O_3, CH_2Cl_2, −78 °C; $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, RT; *n*-Bu_3P, RT; b) BnBr, K_2CO_3, DMF, RT, 60% (2 steps); c) $NiCl_2$, $NaBH_4$, MeOH, CH_2Cl_2, −40 °C; AllocCl, aq. $NaHCO_3$, 0 °C; d) $Pb(OAc)_4$, MeOH, reflux; e) $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, RT; $NaNO_2$, aq. HCl, dioxane, RT, 40% (3 steps); f) PPTS, $MeC(OMe)_3$, MeOH, RT, 78%; g) H_2, Pd/C, MeOH, RT; h) 2,4,6-trichlorobenzoylchloride, Et_3N, toluene, RT; DMAP, RT, 78% (2 steps); i) TMSI, MeCN, 0 °C; j) CbzNC(SMe)NHCbz, $HgCl_2$, Et_3N, CH_2Cl_2, RT, 97% (2 steps); k) TFA, H_2O, 60 °C, 27% (**40**), 46% (**41**); l) H_2, Pd/C, MeOH, RT, 98%; m) H_2, Pd/C, MeOH, RT, 96%. Alloc = allyloxycar-



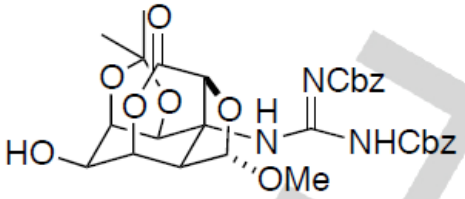
Scheme 5. Divergent synthesis of the TTX congeners. a) TFA, H_2O, RT, 74%; b) $NaIO_4$, MeOH, H_2O, RT; c) $NaBH_4$, MeOH, RT, 66% (2 steps); d) TFA, H_2O, 60 °C, 18% (**44**), 43% (**45**); e) H_2, Pd/C, MeOH, RT, 88%; f) H_2, Pd/C, MeOH, RT, 85%.



42

1) $NaIO_4$
MeOH-H_2O, rt

2) $NaBH_4$
MeOH, 0 °C to rt
66% (2 steps)



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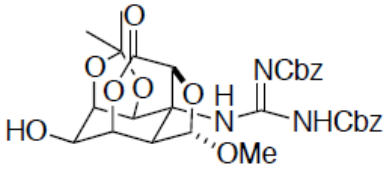
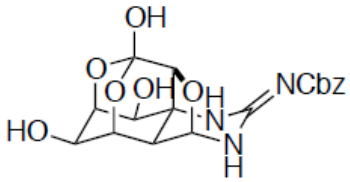
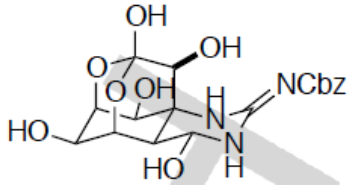


43

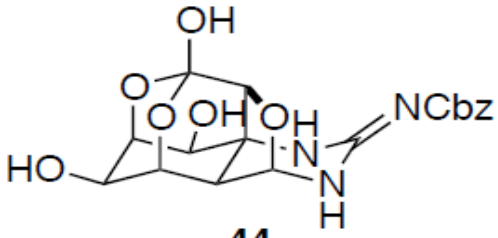
TFA-H_2O
60 °C



44
18%



45
43%

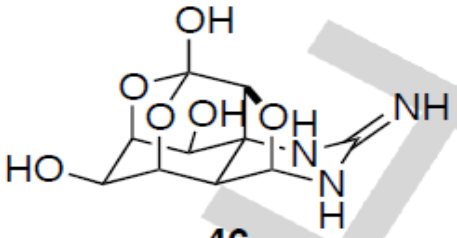


44

H_2, Pd/C

MeOH, rt

88%



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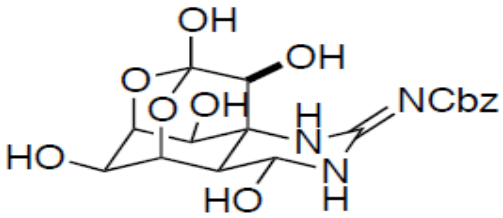
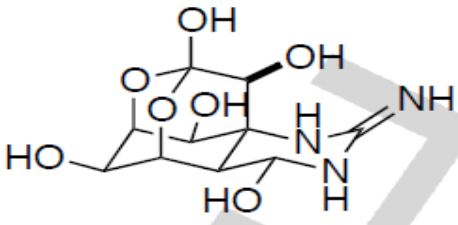


45

H_2, Pd/C

MeOH, rt

85%



7

Synthetic Approach to Tetrodotoxin

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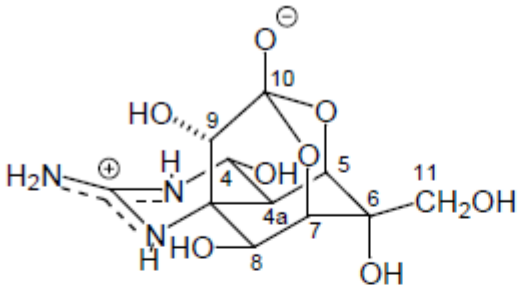
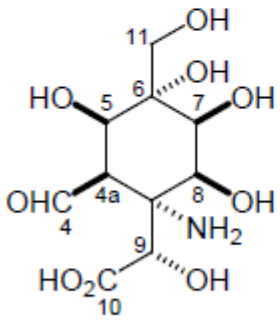
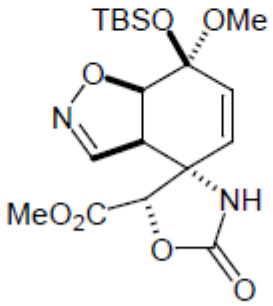


Tetrodotoxin (**1**)



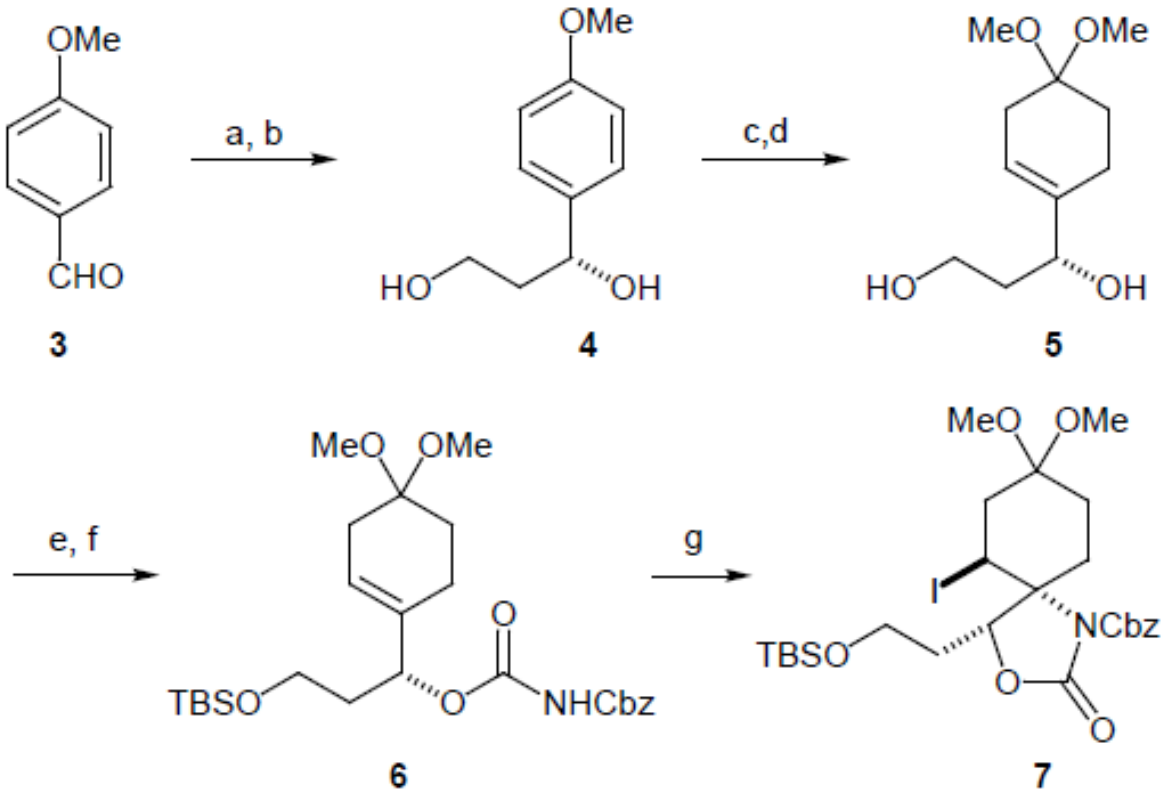
core skeleton of **1**



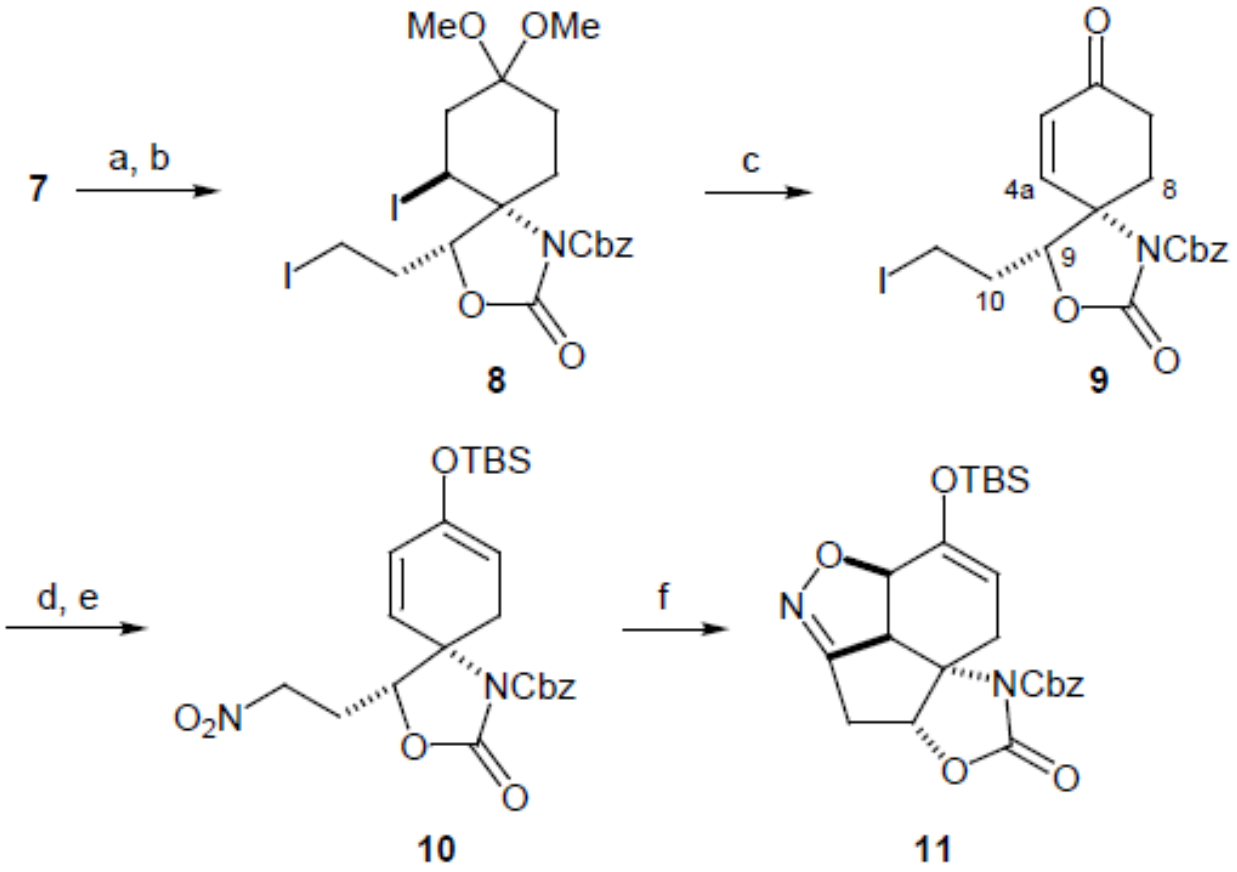
2

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

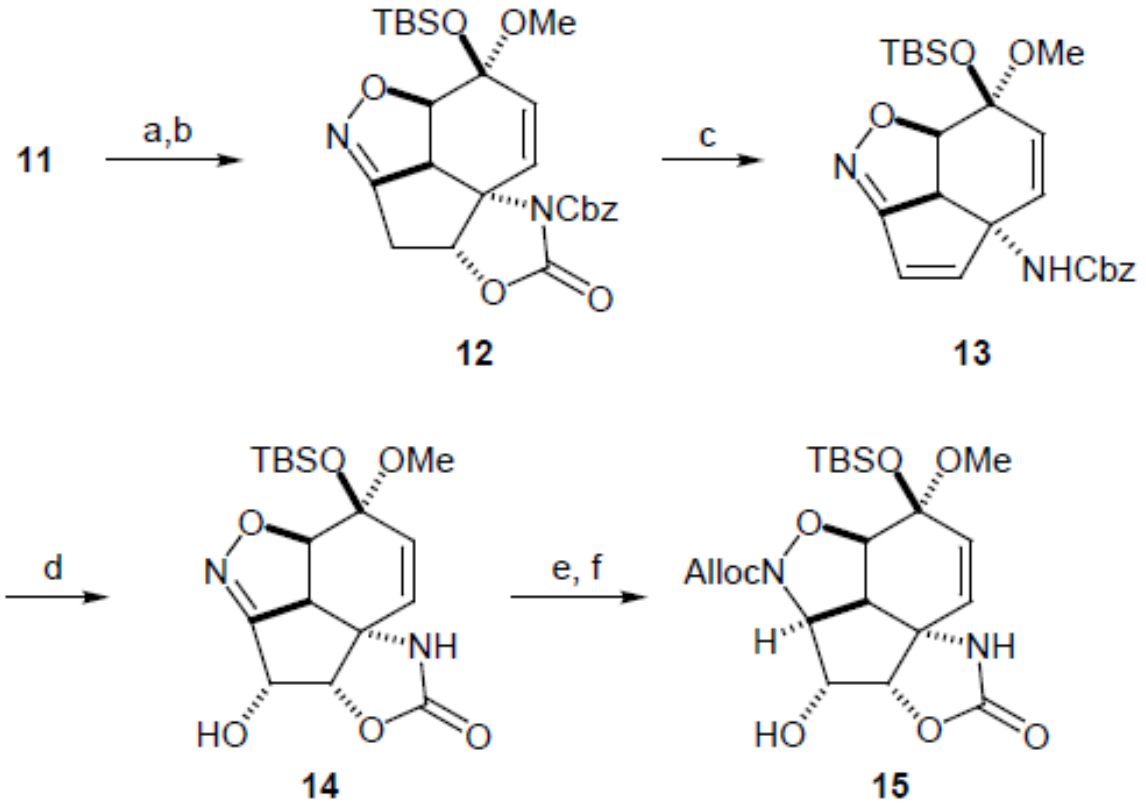
Synlett 2002, No. 8, 1323–1325



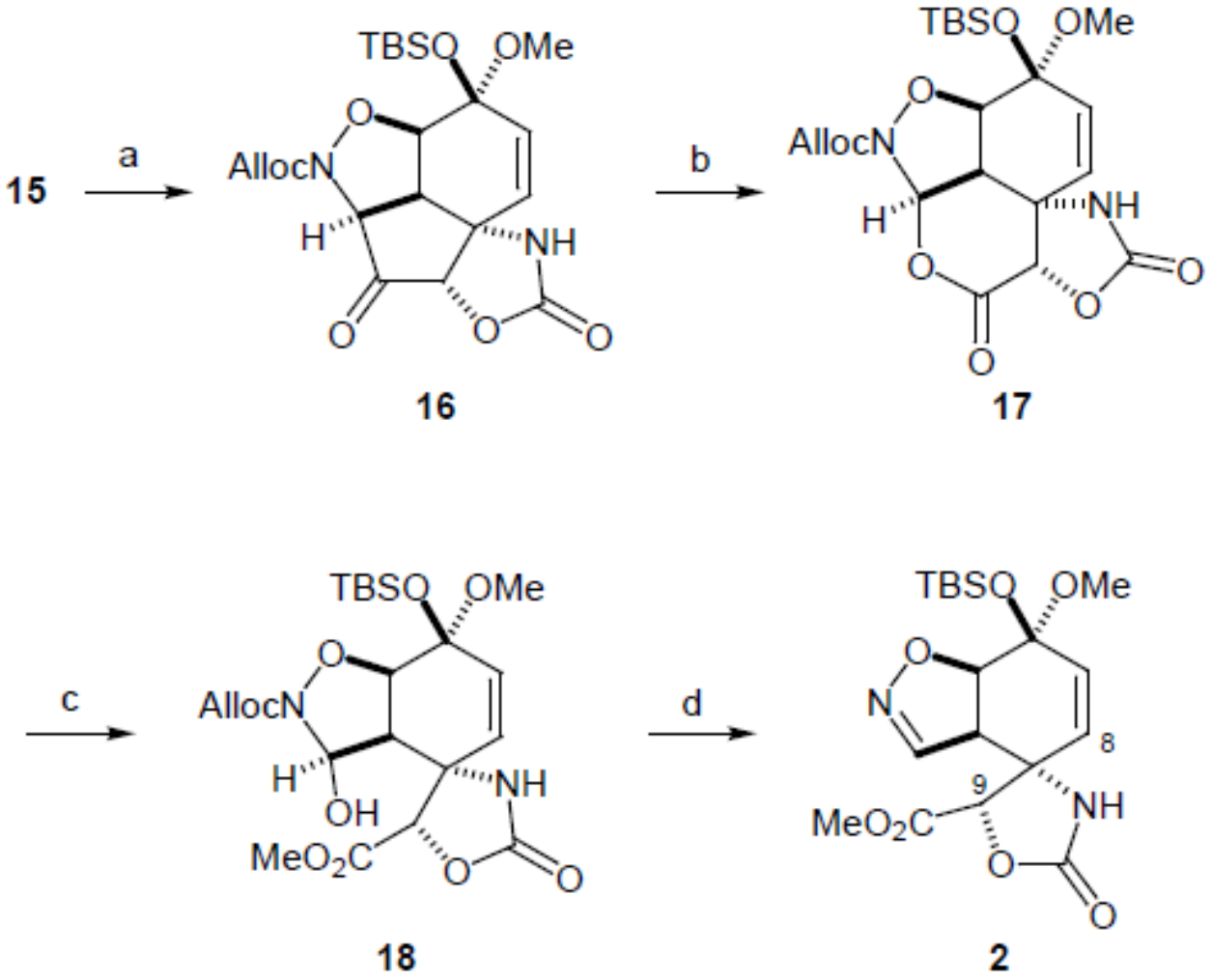
Scheme 1 *Reagents and Conditions:* (a) Allylmagnesium bromide, ether, 0 °C; (b) O_3, CH_2Cl_2–MeOH (1:1), –78 °C; $NaBH_4$, 0 °C; (c) Li, EtOH, THF, liquid NH_3, reflux, 5 min; (d) cat. PPTS, MeOH, r.t., 85% (4 steps); (e) TBSCl, imidazole, CH_2Cl_2, 0 °C. 89%; (f) triphosgene, benzyl carbamate, pyridine,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



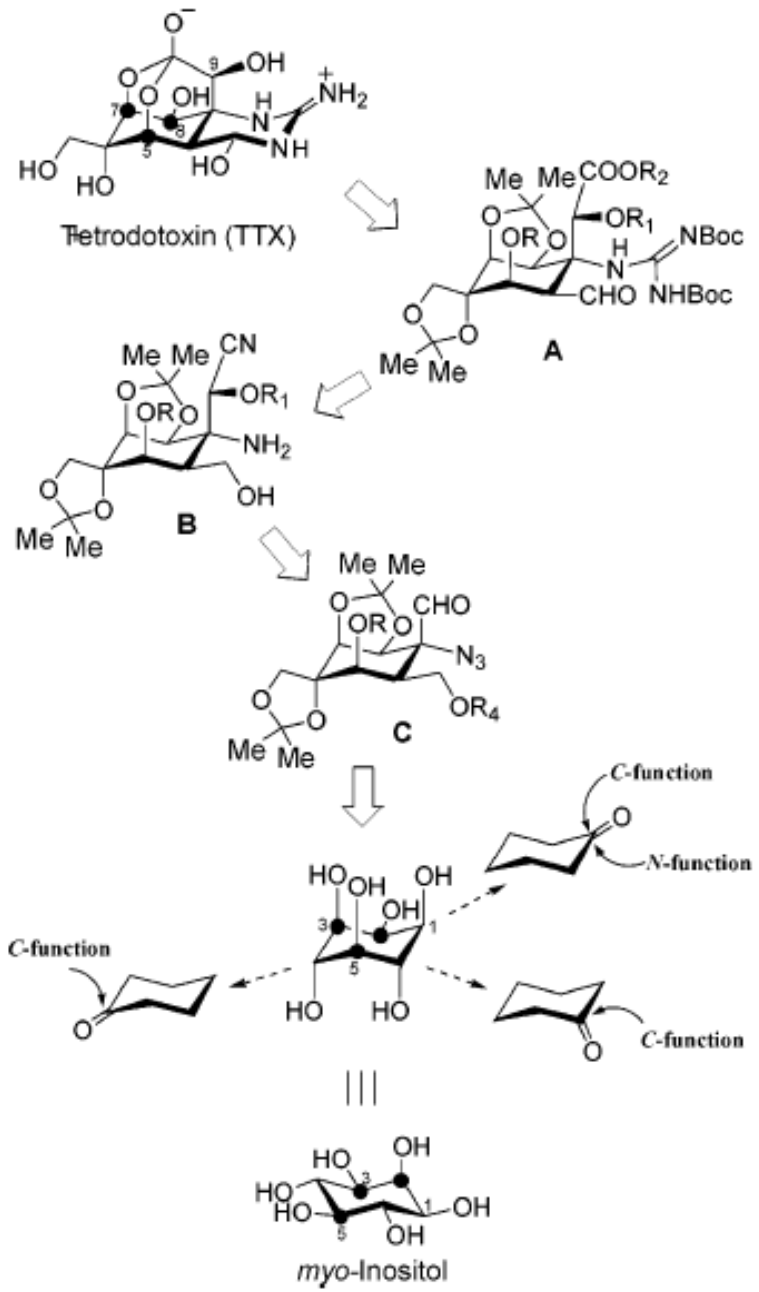
Scheme 2 *Reagents and Conditions:* (a) TBAF, THF, r.t.; (b) PPh_3, I_2, imidazole, benzene, r.t., 54% (3 steps); (c) 80% aq HOAc, 100 °C, quant.; (d) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 89%; (e) $NaNO_2$, DMF, 66%; (f) Boc_2O, cat. DMAP, CH_3CN, 90%.



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%.



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).



J. Org. Chem. **2005**, *70*, 7496-7504

Strategies

Intramolecular Nitrile Oxide Cycloaddition Reactions
Diels-Alder Reactions or Annulation Processes
Carbohydrates and Congeners