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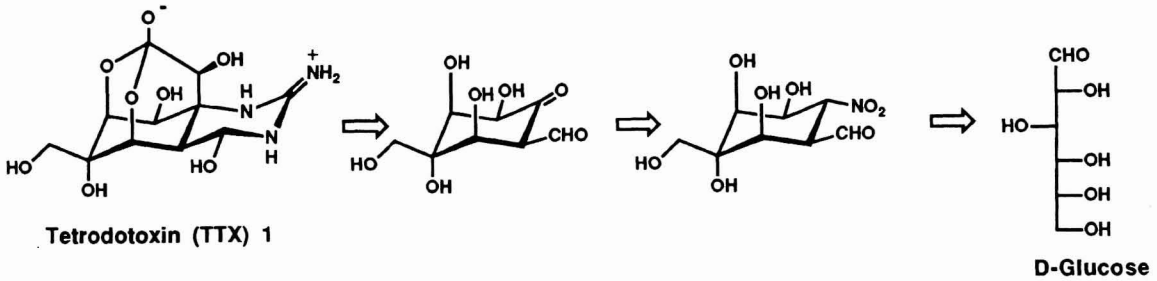
Synthesis of the Functionalized Cyclohexanecarbaldehyde Derivative. A Potential Key Compound for Total Synthesis of Optically Active Tetrodotoxin

Ken-ichi SATO,* Yasuhiro KAJIHARA, Yutaka NAKAMURA, and Juji YOSHIMURA†
Laboratory of Organic Chemistry, Faculty of Engineering,
Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221

Oxidation of 1_L-(1,2,3',4,5/3,6)-3-hydroxymethyl-2,4,5-tri-O-methoxymethyl-3,3'-O-methylene-6-nitro-2,3,4,5-tetrahydroxycyclohexanecarbaldehyde dimethyl acetal with potassium t-butoxide and m-chloroperbenzoic acid has given corresponding carbonyl derivative in 65% yield. The carbonyl compound has been successfully converted into the desired key compound for tetrodotoxin synthesis in excellent yield *via* the spiro α-chloro-epoxide derivative.

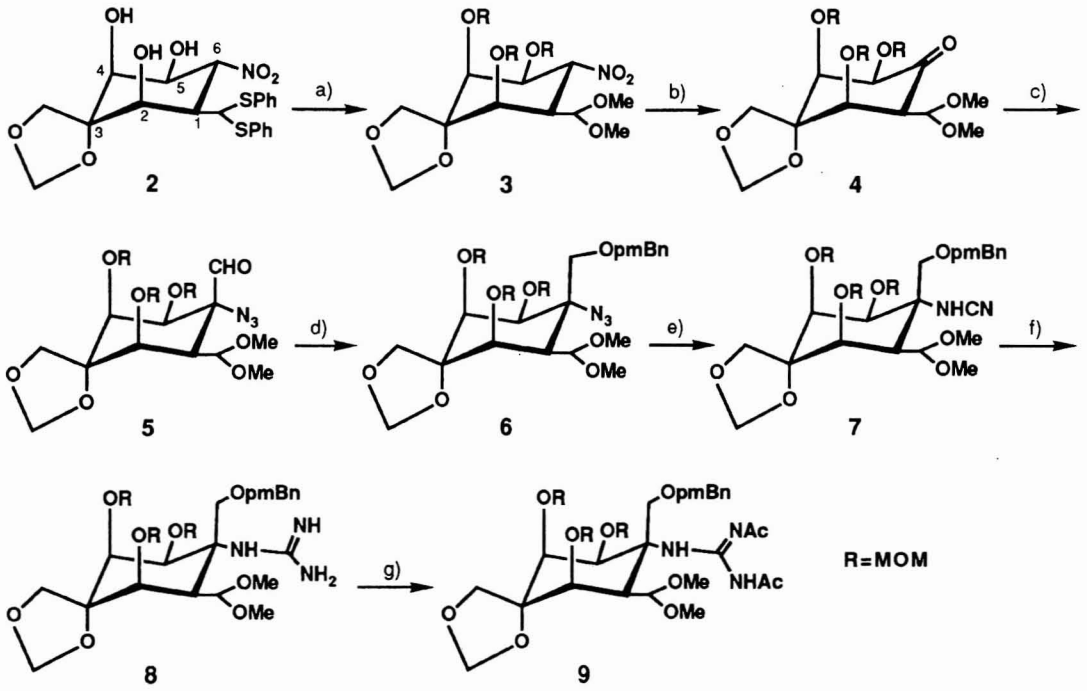
Tetrodotoxin (TTX, **1**) one of the best known marine toxins first isolated from pufferfish[1] and the California newts[2] has recently been found from various biota.[3] TTX has been the subject of investigations for its extremely potent neurotoxicity and unique chemical as well as pharmacological properties. Recently, Isobe et al. reported[4] an elegant approach for TTX synthesis from a sugar derivative, levoglucosenone. We are planning to contribute to pharmacology through organic synthesis of optically active TTX and its analogues[3a,5] in our own pathway (Scheme 1). As a result of many efforts, we succeeded in obtaining a hopeful key compound 1_L-(1,2,3',4,5,6'/3,6)-6-guanidino-3,6-di-hydroxymethyl-6'-O-p-methoxybenzyl-2,4,5-tri-O-methoxymethyl-3,3'-O-methylene-2,3,4,5-tetrahydroxycyclohexanecarbaldehyde dimethyl acetal (**8**) for total synthesis of optically active TTX. In this paper, we would like to communicate a key reaction for obtaining of **8**. (Scheme 2)

In the previous paper,[6] M. Funabashi et al. reported a synthesis of functionalized cyclohexanecabaldehyde trimethylene dithioacetal derivative. In the same manner as adopted by M. Funabashi et al., its bis(phenyl) dithioacetal derivative [**2**: mp 142-144 °C; $[\alpha]_D$ -86.0° (c 1.5, $CHCl_3$)] was prepared in better yield from D-glucose.



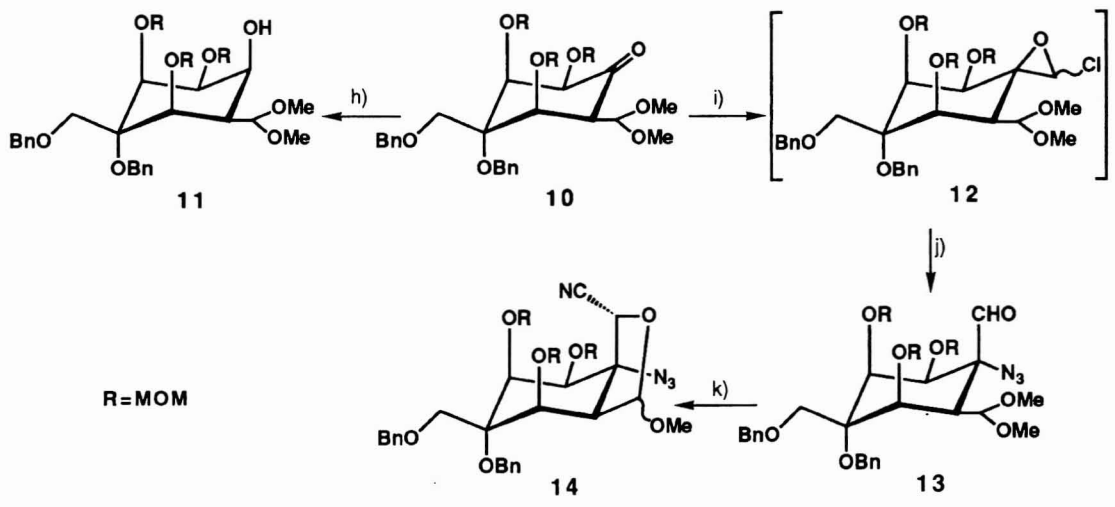
Scheme 1.

† Present address: Department of Basic Science, Iwaki Meisei University, Iino, Chuodai, Iwaki 970.



a) 1. $CH_2(OMe)_2$, $P_2O_5/CHCl_3$, 2. HgO, $HgCl_2$, BF_3OEt_2, $CH(OMe)_3$/ MeOH; b) mCPBA, t-BuOK/Benzene; c) 1. LDA, CH_2Cl_2, THF, -9 0 °C, 2. NaN_3, 15-crown-5/HMPA, 70 °C; d) 1. $NaBH_4$, EtOH, 2. pmBnCl, NaH,/DMF; e) 1. Pd/C-H_2, EtOH, 2. BrCN, $NaHCO_3$/ MeOH-H_2O; f) NH_3aq./ EtOH; g) Ac_2O/Pyridine

Scheme 2.



h) $NaBH_4$/EtOH; i) LDA /CH_2Cl_2,THF,-78 °C; j) NaN_3,15-crown-5 /HMPA,70 °C; k) 1. TMSCN,Et_3N /MeOH, 2. PPTS/CH_2Cl_2

Scheme 3.

Compound **2** was converted into its dimethyl acetal derivative [**3**: mp 70-72 °C; $[\alpha]_D$ -37.6° (c 1.8, $CHCl_3$)] by treatment of **2** with dimethoxymethane and diphosphorous pentoxide, then with mercury (II) chloride and boron trifluoride diethyl ether in dry methanol in 75% yield (2 steps). Many reactions of C-C bond formation at C-6 position in nitro compound **3** were examined, but we did not get successful results. Then compound **3** was converted into cyclohexanone derivative [**4**: mp 106-108 °C; $[\alpha]_D$ +39.8° (c 1.0, $CHCl_3$)] in 82% yield by oxidation with potassium t-butoxide and m-chloroperbenzoic acid in benzene. In 1969, Köbrich, et al. reported an interesting spiro chloroepoxide which gave α–chloro aldehyde and α-hydroxy aldehyde in good yield.[7] We were inspired by Köbrich's work in constructing the α-azido aldehyde for TTX synthesis. The new approach to TTX is based on the stereospecific formation of spiro chloroepoxide derivative from the corresponding carbonyl compound, followed by opening of its three-membered ring in the presence of azide ions.[8a] Our recent studies show that the dichloromethyl group can be introduced by a steric factor and the ring opening with azide ions occurs with complete regiospecificity at β carbon with respect to the chloro group and according to an S_N2 reaction.[8b] The stereochemistry at the quaternary carbon was supported by chemical modifications of benzyl derivative (**10**). (Scheme 3) The carbonyl compound **10** was reduced with sodium borohydride to give the corresponding axial alcohol (**11**) in 83% yield. The results indicate that the stereoselectivity of this nucleophilic reaction to carbonyl compound **10** is controlled by 1,3-diaxial interactions of C-2 and C-4 substituents. In a similar manner as $NaBH_4$, $LiCHCl_2$ seems to attack the carbonyl group from the less hindered side to give the corresponding spiro α–chloroepoxide (**12**). A treatment of **12** with NaN_3 in HMPA gave the azido aldehyde compound (**13**) in 60% yield (from **10**, 2 steps). The compound **13** was converted into the 1:1 mixture of corresponding cyanohydrin derivatives in 82% yield. The more polar cyanohydrin was treated with pyridinium p-toluenesulfonate to give the 2:1 mixture of bicyclic acetal (**14**) in 89% yield. The less polar isomer did not react by the similar treatment. The configuration at C-6' of **14** seems to be (R) according to the above result. And the configuration at C-6 was supported by the respective small coupling constants ($J_{1,1'}$= 0 Hz and $J_{1,1'}$= 4.6 Hz) of the anomeric mixtures of **14**. It seems that the cyanide derivative **14** is a suitable key compound for TTX synthesis. However, some results which we got while studying TTX synthesis show that **14** needs more longer steps than **8** for the total synthesis of TTX. Along the line of TTX synthesis (Scheme 1), we selected the compound **8** as the best intermediate. The compound **8** was prepared in the following way: the carbonyl compound **4** was treated to give the azido aldehyde compound [**5**: mp 60-62 °C; $[\alpha]_D$ -37.2° (c 1.2, $CHCl_3$)] in 79% yield (2 steps) in the same manner as **10** had been treated. A hydride reduction of **5** with sodium borohydride, followed by protection of the hydroxyl group with the p-methoxybenzyl group, gave compound (**6**) in 83% yield. A reduction of the azido group of **6** with Pd/C-H_2 gave the corresponding amino derivative in quantitative yield. The amino compound was treated with cyanogen bromide to give cyanamide derivatives (**7**) in 80% yield. **7** was heated with ammonia to afford the key guanidino compound **8** which was converted into its diacetyl compound [**9**: sirup; NMR ($CDCl_3$); δ 2.05 and 2.13 (each s, 2xOAc), 3.08, 3.14, 3.29, 3.33, 3.37, and 3.80 (each s, 6xOMe), 9.69 and 13.06 (each broad s, 2xNH); MS: m/z 688 (M+H), m/z 656 (M-OMe), treated with NaI; m/z 710 (M+Na)] in 46% yield (2 steps). Thus, a potential key compound **8** was synthesized in optically active form from D-glucose. Further studies on TTX synthesis are in progress.

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