Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8199-8202, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01860-6

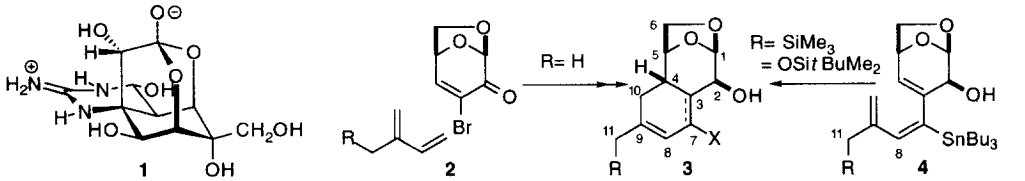
Tin-Assisted Cyclization for Chiral Cyclohexane Synthesis, An Alternative Route to (-)-Tetrodotoxin Skeleton

Makoto Bamba, Toshio Nishikawa and Minoru Isobe*

Laboratory of Organic Chemistry, School of Agricultural Sciences, Nagoya University
Chikusa, Nagoya 464-01, Japan

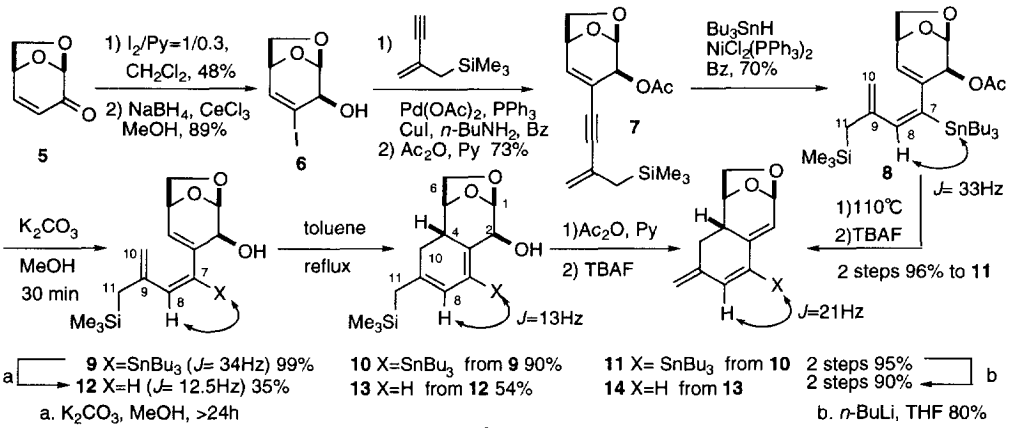
Abstract *: A carbon framework including chiral cyclohexane was synthesized as a possible intermediate for tetrodotoxin. The key steps were electrocyclization of the precursor triene derivatives. Smooth cyclization resulted especially with tributyltin derivative due to an attractive interaction with the 2-oxygen function. The corresponding triethylsilyl derivative scarcely reacted due to rather repulsive interaction.* Copyright © 1996 Elsevier Science Ltd

Tetrodotoxin (**1**) is still a challenging target molecule for synthesis from view points of stereochemical problems of concentrated functional groups and low solubility problem to any organic solvent at the last steps in synthetic reactions. The total synthesis of racemic **1** has been achieved by Kishi since 1972,[1] and several other studies have been reported toward the synthesis of (-)-tetrodotoxin.[2,3] None of the papers have yet reported the synthesis of optically active tetrodotoxin. Continuation of our synthetic efforts toward (-)-tetrodotoxin has based on Diels-Alder cycloaddition between a 1,3-butadiene derivative with bromolevoglucosenone (**2**) for the construction of the chiral cyclohexane ring (**3**).[4] We describe here an alternative route to construct this cyclohexane ring; thus, the key reaction for the construction of the carbon framework not by Diels-Alder cycloaddition reaction but by electrocyclic reaction[5] such as **3** ← **4**. This route would provide us benefit for further functionalization with more freedom for the introduction of R (= $SiMe_3$, OR' etc.).



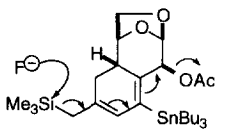
The starting material for the new synthesis is levoglucosenone **5** to examine this cyclization. Addition of iodine to **5** and concomitant elimination of HI,[6] afforded the corresponding α-iodoketone, which was selectively reduced with sodium borohydride-cerium chloride to give the allylic alcohol **6**. An ene-yne coupling between this vinyl iodide **6** and the 2-(trimethylsilylmethyl)but-1-en-3-yne[7] was achieved by palladium catalyst[8] and the product was acetylated to give **7** in 73% overall yield. Hydrostannation of the product acetylene **7** was facilitated with tributyltin hydride in the presence of a nickel catalyst[9] (4 mol% $NiCl_2(PPh_3)_2$ in benzene) to provide the triene **8**. It was treated with potassium carbonate in methanol for half an hour. The stereochemistry of this product triene **9** was proved to be that the tin situated at the 7-position

judging from the nmr experiments; thus, NOESY spectra showed cross peaks between H-8 and H-10, H-8 and H-11, and the coupling constant was J= 34 Hz[10] between H-8 and Sn-7.



Scheme 1

This triene **9** was isolated in 99% yield and then dissolved in toluene and heated at 110°C to afford the cyclization product **10** in 90% yield. Attempted acetylation of its alcohol in **10** yielded a mixture of the corresponding acetate and the triene **11**; then this mixture was further treated with TBAF to give only **11** (probably through mechanism as indicated in **10a**). The tributyltin group of **11** was removed by treatment with *n*-BuLi in THF solvent to give the triene **14**. On the other hand, the hydrostannated product **8** was treated contiguously (without isolation of **8**) with potassium carbonate in methanol solvent for overnight. To our surprise, the similar triene product as **12**[11] was obtained without any tin-group, which showed the *cis*-vinylic protons (J =12.5 Hz). Heating of **12** in refluxing toluene provided the cyclization product **13**. Transformation of **13** into **14** was alternatively facilitated by acetylation and subsequent treatment with TBAF. Direct transformation from **8** to **11** was carried out in one-pot process by successive treatments including heating in refluxing toluene and then stirring with TBAF at rt in 96% yield.

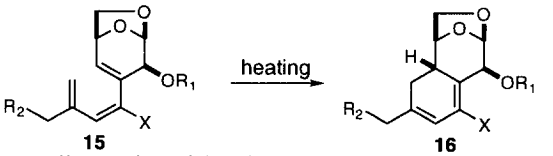


10a

Electrocyclic reaction of the precursor triene **9** or **12** was the critical reaction in the current synthetic studies. We have prepared the eleven analogous trienes **15-1~15-11** (as in Table 1), having different protection or non-protection at the C-2 alcohol (R_1), different atoms of "O, H or Si" at the C-11 position and of "H, Si or Sn" at the C-7 position. Detail of the synthesis of each compound is omitted in this communication, but preparation was achieved in the similar method as described in Scheme 1. The results of cyclization are summarized in Table 1 after heating and under minimum period of reaction time to consume the starting material, respectively.

All the trienes (**15** in Table 1) did cyclize by simple heating to give different result in cyclization. The triene with triethylsilyl group (**15-1** and **-2**) gave only 8 and 20%, respectively even heated for longer than 6 hr. When the tributyltin compound as **15-6** was heated under refluxing in toluene, it cleanly gave a single product (**16-6**) in 90% yield. Whereas the cyclization with protected acetate **15-7** afforded the triene **11** in 33% yield; thus, total yield of cyclization was 81%. The reaction of **15-8** and **15-9** with oxygen function at the C-11 position showed moderate yields. The simple *cis*-vinyl compounds **15-4** and **15-5** afforded the

corresponding cyclization products **16** in modest yields around 50%. These results implied that several factors worked positively or negatively among the R_1, R_2 or X groups. Since the difference between the 2-hydroxy (or 2-acetoxy) groups in **15-6** and that in **15-7** was small, some attractive interaction seems to exist between the tin and oxygen atoms. Difference between entries **15-1** and **15-9** indicates $SnBu_3$ being better than $SiEt_3$. Even in entries **15-5** and **15-11**, the latter (X= $SnBu_3$) gave better result than the former (X=H). In addition to above rational of attractive interaction between the tin and oxygen atoms, an opposite repulsive interaction is observed with C-7 silyl group, while compounds (**15-4, 5**) X= H showed intermediate results. This tendency of cyclization by the effect with X (X= $SnBu_3$ > H > $SiEt_3$) is also withdrawn from experiments among **15-3**, **15-4** and **15-6**. In addition to this, allylsilanes are more reactive than allyl alcohols.



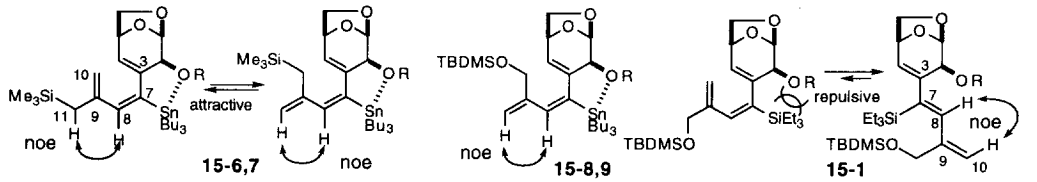
15 **16**

Table 1 Results of electrocyclic reaction of the triene into the cyclohexadiene.

15	R_1	R_2	X	solvent	hr	yield of **16** (%)
15-1	Ac	$OSiMe_2tBu$	$SiEt_3$	xylene	>6	8
15-2	Ac	$SiMe_3$	$SiEt_3$	xylene	3.0	20
15-3	H	$SiMe_3$	$SiEt_3$	xylene	3.0	34
15-4	H	$SiMe_3$	H	toluene	3.0	54
15-5	H	H	H	toluene	1.0	51
15-6	H	$SiMe_3$	$SnBu_3$	toluene	0.2	90
15-7	Ac	$SiMe_3$	$SnBu_3$	toluene	0.2	81#
15-8	H	$OSiMe_2tBu$	$SnBu_3$	xylene	3.0	47
15-9	Ac	$OSiMe_2tBu$	$SnBu_3$	xylene	3.0	49
15-10	Ac	OH	$SnBu_3$	xylene	2.0	51
15-11	H	H	$SnBu_3$	xylene	2.0	71

Compounds **15** were heated in refluxing toluene or heated in xylene at bath temp 150 °C in the presence of a small amount of WX-R {4,4'-thiobis(6-*tert*-butyl-3-methylphenol)} as sumilizer. # Yields are of cyclization including 33% of **11**.

Reactivity of the cyclization depends on geometric factors, *s-cis/s-trans* orientation of the 2 single bonds (C3/C7 and C8/C9) in the triene system. NOE data of the following triene compounds, in fact, provided the information of C8/C9; thus, allylsilanes (**15-6, 7**) showed the noe between H-8/H-11 and H-8/H-10. These data indicate that C8/C9 bond exists in both *s-cis* and *s-trans*. On the other hand, 11-oxy compounds **15-8, 9** showed only noe between H-8/H-10, indicating that C8/C9 is largely *s-trans*. The 11-oxy compound **15-1** showed only H-8/H-10 both being *s-trans/s-trans* orientation.



One of the cyclization products **16-4**(=**13** in Scheme 1) was further functionalized into compounds such as **19**, **20** (Scheme 2). After acetylation of **16-4**, subsequently epoxidation of allylsilane moiety with

MCPBA, treatment with 2*N* HCl in aqueous THF, the desired terminal olefin **17a** was obtained in 80% overall yield. Treatment of the acetate (**17b**) of this allylic alcohol **17a** with osmium tetroxide and NMO gave the diol **19** exclusively. An isomer **20** was obtained in 40% yield from **17a**, *via* epoxidation (**18a**), acetylation (**18b**) and acidic opening of the epoxide ring.

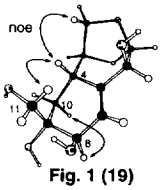
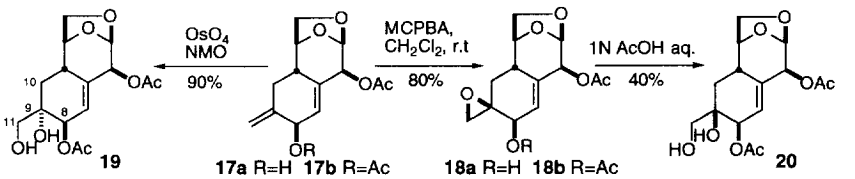


Fig. 1 (19)

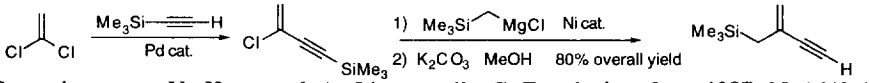


Scheme 2

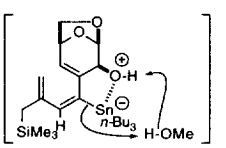
The new stereocenters (the C-8 and 9 positions) were established by nmr analysis; thus, the NOESY spectrum of **19** shows cross peaks between H-8 and H-10, H-4 and H-11 (Fig. 1). Some of these compounds would be of extreme importance as intermediates toward the total synthesis of (-)-tetrodotoxin in our laboratory.

REFERENCES AND NOTES

1. Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.*, **1972**, *94*, 9217-9219. Kishi, Y. *et al.* ibid., **1972**, *94*, 9219-9221.
2. (a) Fraser-Reid, B.; Alonso, R. A.; McDevitt, R. E.; Rao, B.; Venkateswara; Vite, G. D.; Zottola, M. A. *Bull. Soc. Chim. Belg.* **1992**, *101(7)*, 617-626. (b) Alonso, R. A.; Burgey, C. S.; Rao, B. Venkateswara; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.*, **1993**, *115(15)*, 6666-6672. (c) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.*, **1996**, *61*, 1609-1618.
3. Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.*, **1991**, 1559-1562.
4. (a) Yamamoto, N.; Isobe, M. *Tetrahedron*, **1993**, *49*, 6581-6590. (b) Yamamoto, N.; Isobe, M. *Chem. Lett.*, **1994**, 2299-2302. (c) Yamamoto, N.; Nishikawa, T.; Isobe, M. *Synlett, (Special Issue for Prof. Stork)*, **1995**, 505-506; and references therein.
5. Okamura, W. H.; Delera, A. R. In Comp. Org. Syn. *5* section 6.2.2. pp706-730, *Pergamon Press*.
6. (a) Bovonsombat, P.; Angara, G. J.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787-6790. (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayke, C. B. W.; Workulick, P. M.; Uskokovic, M. R.; *Tetrahedron Lett.* **1992**, *33*, 917-918.
7. The 2-(trimethylsilyl)methyl-but-1-en-3-yne was synthesized in 3 steps (i) by a coupling between the corresponding 1,1-dichloroethylene and trimethylsilylacetylene in the presence of palladium as catalyst: and (ii) by the coupling reaction between trimethysilylmethylmagnesium chloride and 2-chloro-4-trimethylsilyl-but-1-en-3-yne in the presence of a nickel catalyst, (iii) desilylation.



(a) Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.*, **1987**, *28*, 1649-1650. (b) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.*, **1979**, *20*, 429-432.
8. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, *16*, 4467-4470.
9. (a) Nativi, C.; Taddei, M. *J. Org. Chem.*, **1988**, *53*, 820-826. (b) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.*, **1988**, 881-884. (c) Miyake, H.; Yamamura, K. *Chem. Lett.*, **1989**, 981-984.
10. The stereochemistry of the addition was apparent from the ^{1}H NMR spectra by examination of the Sn-H coupling constant; typically, when the proton and tin were *cis*, J ~70 Hz and when they were *trans*, J ~120 Hz. See: Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organometal. Chem.*, **1967**, *9*, 285-294.
11. The possible intermediate such as **9a** from the once-isolated **9** did not give the destannated product **12** nor **13**. The detail of this mechanism is still open.



9a

(*Received in Japan* 28 *August* 1996; *accepted* 17 *September* 1996)