

Relative Configuration of a Marine Toxin Polycavernoside-A

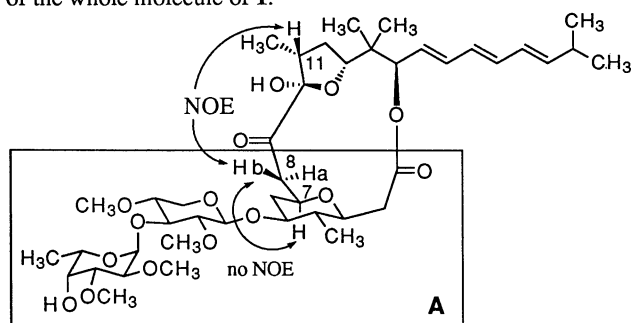
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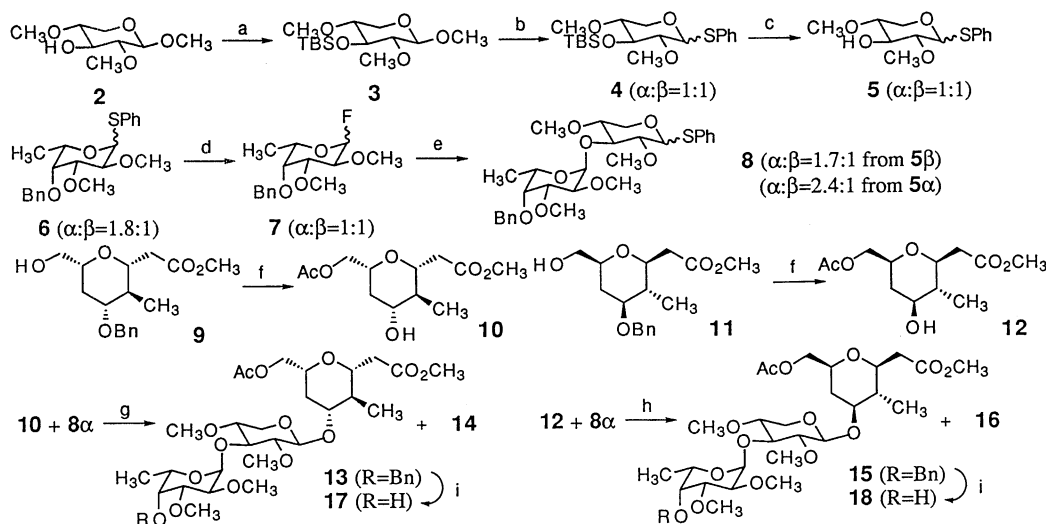
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Combination of the sugar and tetrahydropyran parts of polycavernoside-A, which has been isolated as one of toxic principles from the red alga *Polycavernosa tsudai*, revealed the whole relative configuration of the compound from the spectral data.

The title compound (**1**) has been isolated as one of the sources of human intoxication from the red alga *Polycavernosa tsudai* by Yasumoto et al. in 1993.¹ Although they have reported the planar structure of **1**, only the respective relative configurations of the tetrahydrofuran ring, the tetrahydropyran ring, and the respective sugar moieties have been clarified. Very recently, we have concluded that the disaccharide moiety of **1** consists of a combination of D-xylose and L-fucose or their enantiomers.² In this paper, we describe the combination of the disaccharide with both enantiomers of the tetrahydropyran rings³ leading to the formation of the segment A and the corresponding diastereoisomer in order to establish the relative configuration of the whole molecule of **1**.

Polycavernoside-A (**1**)

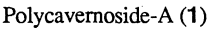
The hydroxyl group of compound **2**,² derived from natural D-xylose in a 66.6% overall yield, was protected with TBSOTf to give **3** in 98% yield (Scheme 1). By the modification of Hanessian's method,⁴ compound **3** was converted into a 1:1 mixture of phenylthio isomers **4** in a 72% combined yield, which were detached to afford a separable 1:1 mixture of **5** in 95% yield. On the other hand, a mixture ($\alpha:\beta=1.8:1$) of **6**⁵ was allowed to react with diethylaminosulfur trifluoride and NBS⁵ to give an inseparable 1:1 mixture of **7** in a 82% combined yield. According to the Nicolaou's and Kunz's procedures,⁶ compound **7** (1:1 mixture, 1.5 eq) and the β -anomer of **5** (**5 β** , 1 eq) were treated with $\text{BF}_3\cdot\text{OEt}_2$ and MS4A in CH_2Cl_2 at 0 °C for 20 min to afford a separable mixture ($\alpha:\beta=1.7:1$) of disaccharides **8** in an 86% combined yield. The reaction of **7** and the α -anomer of **5** (**5 α**) under the same conditions as above gave rise to **8** as a mixture ($\alpha:\beta=2.4:1$) in an 86% combined yield. In both cases, the configuration of the anomeric carbons at C-1 of the fucose parts in **8 α** (α -SPh at C-1 of the xylose part) and **8 β** (β -SPh) was deduced to be α exclusively from their $^1\text{H-NMR}$ data.⁷ On the other hand, the tetrahydropyranyl ether (**9**), which was prepared from (*S*)-(-)-glycidol,³ was acetylated followed by hydrogenolysis to afford the diol monoacetate (**10**) in a 97% overall yield. The corresponding enantiomer (**11**)³ was transformed likewise into **12** in an 86% overall yield. Glycosidation reactions using **10** or **12** were carried out according to Nicolaou's procedure.⁸ To the cold suspension of **10** (1 eq), **8 α** (1.5 eq), and MS4A in CH_3CN , was added NBS (1.5 eq) at -40 °C~-45 °C and the mixture was stirred for 1 min. After removal of succinimide by washing with water, the residue was separated by SiO_2 column



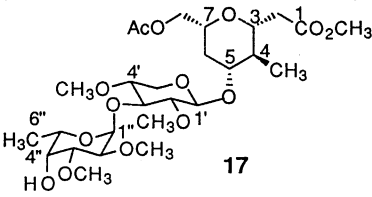
Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C, 2 h, 98%; b) PhTMS, ZnI_2 , $\text{Bu}_4\text{N}^+\text{I}^-$, $(\text{CH}_2\text{Cl})_2$, 60 °C, 1.5 h, 72%; c) TBAF, THF, 25 °C, 3 h, 95%; d) $(\text{C}_2\text{H}_5)_2\text{NSF}_3$, NBS, CH_2Cl_2 , -15 °C, 30 min, 82%; e) $\text{BF}_3\cdot\text{OEt}_2$, MS4A, CH_2Cl_2 , 0 °C, 20 min, 86% from **5 β** and 86% from **5 α** ; f) AcCl , Py, CH_2Cl_2 , 0 °C, 15 min, 100%; g) H_2 , 10% Pd-C, MeOH, 25 °C, 13 h, 97% from **9**, 87% from **11**; h) NBS, MS4A, CH_3CN , -40~-45 °C, 1 min, 66% (**13**) and 34% (**14**); i) NBS, MS4A, CH_3CN , -40 °C, 8 min, 74% (**15**) and 26% (**16**); j) H_2 , 10% Pd-C, MeOH, 25 °C, 12 h~3 d, 82% from **13**, 80% from **15**.

Scheme 1.

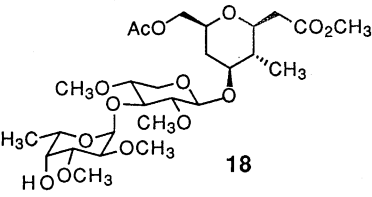
Table 1. Comparison of ^1H -NMR chemical shifts (δ) and coupling constants (J-values in Hz) of natural polycavernoside-A (**1**) and the synthetic glycosides (**17** and **18**)



Polycavernoside-A (**1**)



17



18

position	δ_1^a	δ_{17}^b	$ \delta_1 - \delta_{17} $	δ_{18}^b	$ \delta_1 - \delta_{18} $
4	1.27 (m)	1.31 (tq, 10.1, 6.6)	0.04	1.36 (tq, 10.1, 6.6)	0.09
5	3.33 (dt, 4, 11)	3.40~3.48 (m)	~0.11	3.33~3.38 (m)	~0.02
6	1.37 (q, 11)	1.19 (br q, 11.4)	0.18	1.29 (br q, 11.8)	0.08
	2.05 (dd, 11, 4)	2.04 (ddd, 1.8, 4.8, 12.3)	0.01	1.97 (ddd, 2.0, 4.8, 12.6)	0.08
4-CH ₃	0.93 (d, 7)	0.89 (d, 6.6)	0.04	0.94 (d, 6.5)	0.01
1'	4.32 (d, 8)	4.35 (d, 7.5)	0.03	4.32 (d, 7.7)	0
2'	2.88 (dd, 10, 8)	2.89 (dd, 7.5, 9.2)	0.01	2.88 (dd, 7.7, 9.2)	0
3'	3.44 (t, 10)	3.40~3.48 (m)	0	3.44 (brt, 8.8)	0
4'	3.13 (dt, 4, 10)	3.14 (dt, 4.7, 9.5)	0.01	3.13 (ddd, 4.4, 8.7, 9.9)	0
5'	3.07 (t, 10)	3.08 (dd, 9.7, 10.6)	0.01	3.07 (br t, 10.2)	0
	3.93 (dd, 4, 10)	3.94 (dd, 4.4, 10.8)	0.01	3.93 (dd, 4.4, 10.7)	0
1''	5.21 (d, 4)	5.22 (d, 3.3)	0.01	5.21 (d, 3.3)	0
2''	3.36 (dd, 4, 11)	3.30~3.40 (m)	~0.01	3.35 (dd, 3.3, 10.0)	0.01
3''	3.37 (d, 11)	3.30~3.40 (m)	~0.02	3.37 (dd, 2.7, 10.0)	0
4''	3.79 (br s)	3.79 (br s)	0	3.79 (br s)	0
5''	4.13 (q, 7)	4.13 (br q, 6.6)	0	4.13 (br q, 6.5)	0
6''	1.07 (d, 7)	1.07 (d, 6.6)	0	1.07 (d, 6.6)	0
2'-OCH ₃	3.48 (s)	3.43 (s)	0.05	3.48 (s)	0
4'-OCH ₃	3.31 (s)	3.31 (s)	0	3.31 (s)	0
2''-OCH ₃	3.38 (s)	3.37 (s)	0.01	3.38 (s)	0
3''-OCH ₃	3.34 (s)	3.34 (s)	0	3.34 (s)	0

^a Yasumoto et al.¹

^b ^1H -NMR spectra were measured at 400 MHz in CD₃CN (CHD₂CN as 1.9 ppm).

chromatography to give β - (**13**) and α -glycosides (**14**) in 66% and 34% yields, respectively. The reaction of the enantiomer (**12**, 1 eq) and **8** α (1.5 eq) under the similar conditions at -40 °C for 8 min yielded the diastereomeric β - (**15**) and α -glycosides (**16**) in 74% and 26% yields, respectively. The respective β -glycosides (**13** and **15**) were converted on hydrogenolysis with Pd-C in MeOH into the desbenzyl derivatives (**17**⁹ and **18**¹⁰) in 82% and 80% yields, respectively. The ^1H -NMR spectral data of these glycosides in CD₃CN (400 MHz) were shown in Table 1 with those of **1**.¹ The comparison reveals that the chemical shifts of the protons on the tetrahydropyran parts in **17** and **18** gave rise to apparent deviations from those of **1**, because of the presence of acetoxy and methoxycarbonyl groups being different from **1**. However, when the chemical shifts of the protons at C5 and C4-CH₃ are compared, both the differences from **1** are less in **18**. Furthermore, all the chemical shifts at the proton at C1' and the protons of OCH₃ groups at C2', C4', C2'', and C3'' are much more coincident in **18** with those of **1**. In the chemical shifts and splitting patterns of the residual protons in the disaccharide moiety, no deviation was observed in **18** than in **17**. Accordingly, combining with the nOe experiments between H7 and H8b or H11 and H8b on tetrahydrofuran ring and tetrahydropyran ring in **1** as well as the coupling constants between H7 and H8a (0 Hz) or H7 and H8b (9 Hz),¹ we could conclude that the relative configuration of the whole molecule of polycavernoside-A should be revised as indicated in **1**, which is different from the tentative proposal by Yasumoto et al.¹ It has been well known that the xylose has always been detected

as the D-form from marine sources. Thus we propose further the absolute configuration of polycavernoside-A as **1**.

References and Notes

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- 7 For ^1H -NMR data of C-1 protons on the fucose parts, **8** α : δ_{H} 5.41 (d, J=3.4 Hz); **8** β : δ_{H} 5.36 (d, J=3.7 Hz).
- 8 K. C. Nicolaou, S. P. Seitz, and D. P. Papahatjis, *J. Am. Chem. Soc.*, **105**, 2430 (1983).
- 9 **17**: a colorless amorphous; $[\alpha]_{\text{D}}^{24}$ -108.0° (c=1.26, CHCl₃).
- 10 **18**: a colorless amorphous; $[\alpha]_{\text{D}}^{24}$ -84.6° (c=0.72, CHCl₃).