Relative Configuration of a Marine Toxin Polycavernoside-A

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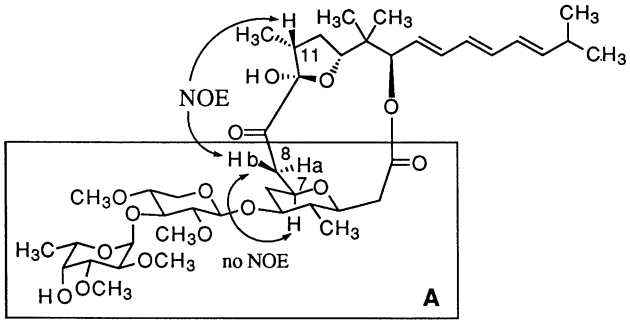
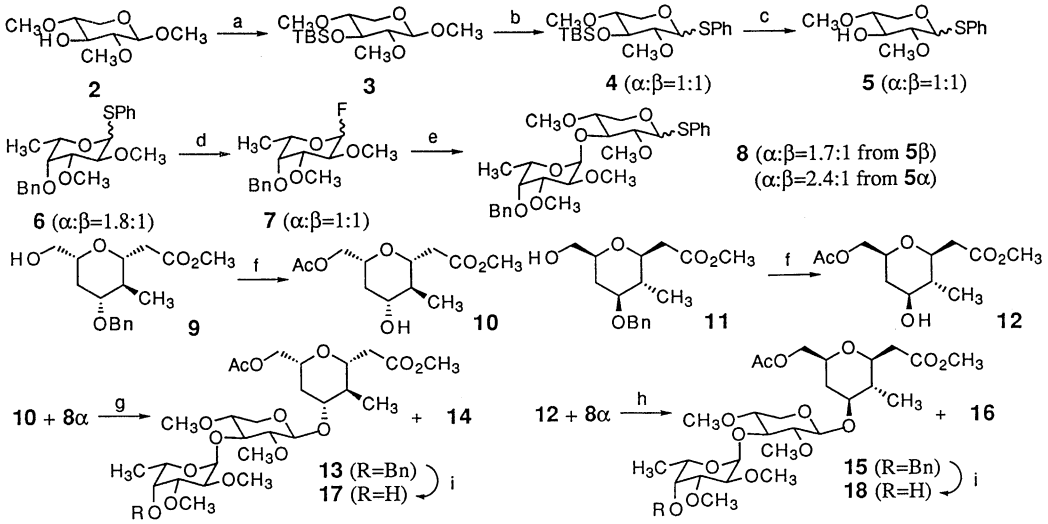
Combination of the sugar and tetrahydropyran parts of polycavernoside-A, which has been isolated as one of toxic principles from the red alga *Polycavernosa tsudai*, revealed the whole relative configuration of the compound from the spectral data.

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 enantioisomers.[2] In this paper, we describe the combination of the dissaccharide with both enantioisomers of the tetrahydropyran rings[3] 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 (α:β=1.8:1) of **6**[2] was allowed to react with diethylaminosulfur trifluoride and NBS[5] 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** (**5β**, 1 eq) were treated with BF_3·OEt_2 and MS4Å in CH_2Cl_2 at 0 °C for 20 min to afford a separable mixture (α:β=1.7:1) of disaccharides **8** in an 86% combined yield. The reaction of **7** and the α-anomer of **5** (**5α**) under the same conditions as above gave rise to **8** as a mixture (α:β=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 **8α** (α-SPh at C-1 of the xylose part) and **8β** (β-SPh) was deduced to be α exclusively from their ^{1}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 enatiomer (**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), **8α** (1.5 eq), and MS4Å 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

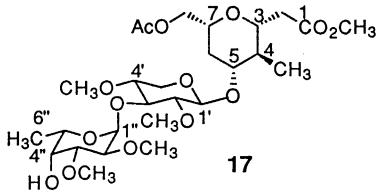


Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 98%; b) PhSTMS, ZnI_2, Bu_4N^+T, $(CH_2Cl)_2$, 60 °C, 1.5 h, 72%; c) TBAF, THF, 25 °C, 3 h, 95%; d) $(C_2H_5)_2NSF_3$, NBS, CH_2Cl_2, -15 °C, 30 min, 82%; e) BF_3·OEt_2, MS4Å, CH_2Cl_2, 0 °C, 20 min, 86% from 5β and 86% from 5α; f) AcCl, Py, CH_2Cl_2, 0 °C, 15 min, 100%; H_2, 10% Pd-C, MeOH, 25 °C, 13 h, 97% from **9**, 87% from **11**; g) NBS, MS4Å, CH_3CN, -40~-45 °C, 1 min, 66% (**13**) and 34% (**14**); h) NBS, MS4Å, CH_3CN, -40 °C, 8 min, 74% (**15**) and 26% (**16**); i) H_2, 10% Pd-C, MeOH, 25 °C, 12 h~3 d, 82% from **13**, 80% from **15**.

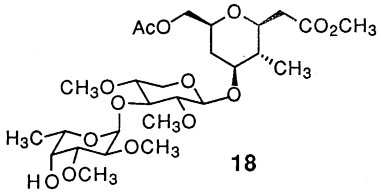
Scheme 1.

Table 1. Comparison of ^{1}H-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]	$\lvert\delta_1 - \delta_{17}\rvert$	δ_{18}[b]	$\lvert\delta_1 - \delta_{18}\rvert$
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] ^{1}H-NMR spectra were measured at 400 MHz in CD_3CN (CHD_2CN 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 ^{1}H-NMR spectral data of these glycosides in CD_3CN (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 acetoxyl and methoxycarbonyl groups being different from **1**. However, when the chemical shifts of the protons at C5 and C4-CH_3 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 OCH_3 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**[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 ^{1}H-NMR data of C-1 protons on the fucose parts, **8**α: δ5.41 (d, J=3.4 Hz); **8**β: δ5.36 (d, J=3.7 Hz).

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9 **17**: a colorless amorphous; $[\alpha]_D^{24}$ -108.0° (c=1.26, $CHCl_3$).

10 **18**: a colorless amorphous; $[\alpha]_D^{24}$ -84.6° (c=0.72, $CHCl_3$).