Synthesis and Relative Configuration of the Sugar Part of a Marine Toxin Polycavernoside-A

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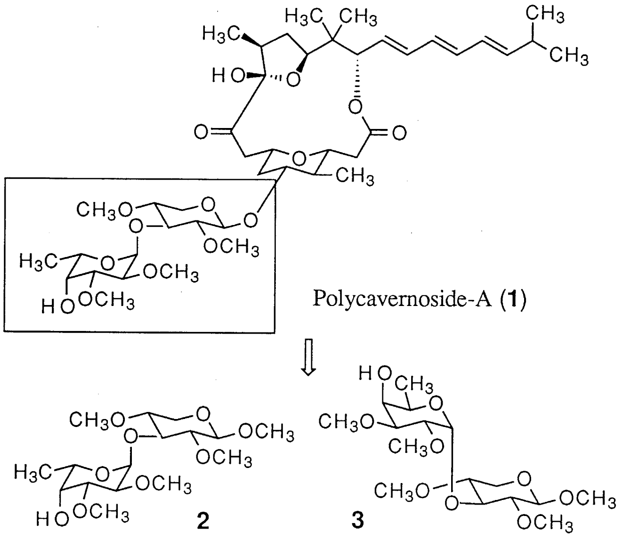
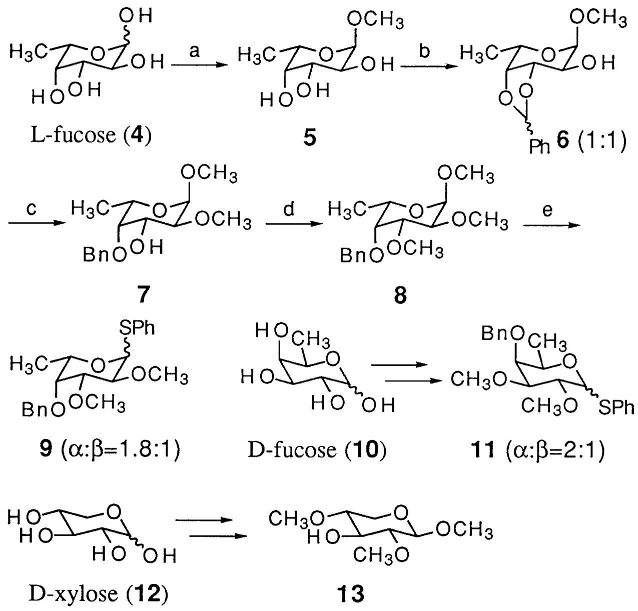
Construction of the sugar part of polycavernoside-A, which has been isolated as one of toxic principles from the red alga *Polycavernosa tsudai*, is described starting from L-fucose and D-xylose in order to elucidate the relative stereochemistry.

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 proposed 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 and the absolute configuration of the whole molecule including the disaccharide part has not been established yet. We have recently reported the syntheses of the tetrahydrofuran[2] and tetrahydropyran parts.[3] We describe herein the construction of disaccharides **2** and **3** corresponding to the possible sugar moiety of **1**.



Polycavernoside-A (**1**)

2 **3**



L-fucose (**4**) **5** **6** (1:1)

7 **8**

9 (α:β=1.8:1) D-fucose (**10**) **11** (α:β=2:1)

D-xylose (**12**) **13**

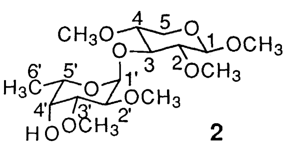
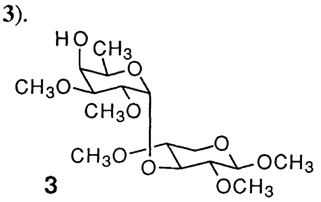
Reagents and conditions: a) CH_3OH, TsOH, reflux, 24 h, 95%; b) $PhCH(OCH_3)_2$, TsOH, CH_3CN, 20 °C, 24 h, 95%; c) CH_3I, *t*-BuOK, THF, 20 °C, 2 h, 91%; DIBAH, CH_2Cl_2, 0 °C, 3 h, 96%; d) CH_3I, *t*-BuOK, THF, 20 °C, 2 h, 93%; e) PhSTMS, TMSOTf, CH_2Cl_2, 20 °C, 24 h, 96%.

Scheme 1.

The synthesis commenced with derivation of natural L-fucose **4**, unnatural D-fucose **10**, and natural D-xylose **12**, all of wich are commercially available (Scheme 1). According to the Bundle's procedure,[4] L-fucose **4** was converted into the methyl acetal **5**, mp 157.0~158.0 °C, and into a 1:1 diastereomeric mixture of 3,4-benzylidene acetal **6** in a 90.3% overall yield. The mixture **6** was methylated with CH_3I and *t*-BuOK and reduced with DIBAH in CH_2Cl_2 at 0 °C for 3 h to afford 4-benzyl ether **7** as an oil, $[\alpha]_D^{18}$ -109.0° (c=1.92, $CHCl_3$), in an 87.4% overall yield. The hydroxyl group at C-3 of **7** was methylated further to afford **8**, oil, $[\alpha]_D^{20}$ -92.7° (c=0.48, $CHCl_3$). The methyl acetal at C-1 of **8** was then allowed to react with PhSTMS and TMSOTf, yielding a separable 1.8:1 mixture of phenylthio acetals **9** in an 89.3% overall yield. The synthesis involved 6 steps and the overall yield amounted to 70.5%. Likewise, unnatural D-fucose **10** was transformed into a separable 2:1 mixture of **11** in a 31% overall yield. Next, preparation of **13** was accomplished by a modification of the Ferrier's procedure[5] from natural D-xylose **12** in a 66.6% overall yield[6] (Scheme 1).

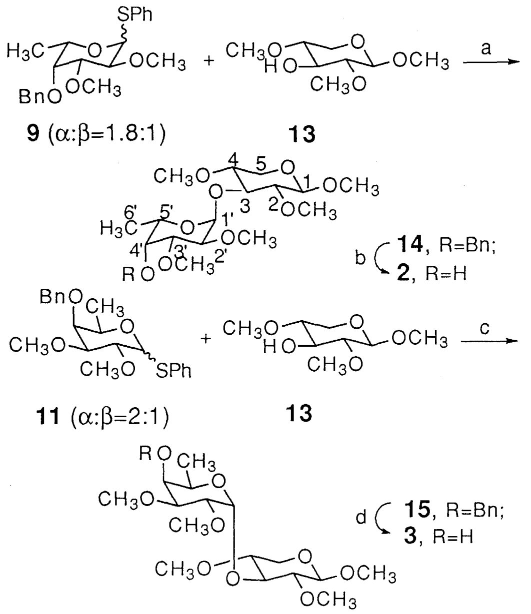
The coupling reactions of **9** or **11** with **13** were carried out by the modification of Veeneman's and Fraser-Reid's procedures[7] (Scheme 2). To the solution of **9** (1.2 eq) and **13** (1.0 eq) in CH_2Cl_2 cooled to -18 °C, were added NBS (1.2 eq) and then Et_3SiOTf (0.5 eq), and the mixture was stirred at -18 °C for 10 min. The reaction effected the coupling to give a mixture (α:β=3.3:1) of the coupled products from which the desired α-compound **14** was isolated practically in 65% yield; **14**, colorless needles, mp 107~108 °C (hexane); $[\alpha]_D^{22}$ -55.1° (c=0.72, $CHCl_3$). The compound was further transformed on hydrogenolysis into **2** in 70% yield; **2**, colorless needles, mp 119~121 °C (hexane); $[\alpha]_D^{18}$ -75.0° (c=0.94, $CHCl_3$). On the other hand, the reaction of **11** (1.2 eq) and **13** (1.0 eq) under the same conditions as above proceeded in the same way to give a mixture (α:β=2.3:1) of the coupled product, from which the desired α-compound **15** was isolated in 68% yield; **15**, colorless amorphous; $[\alpha]_D^{18}$ +51.6° (c=0.52, $CHCl_3$). The compound was transformed to the debenzylated product **3** in 70% yield; **3**, colorless amorphous; $[\alpha]_D^{18}$ +68.5° (c=1.45, $CHCl_3$). The ^{1}H-NMR spectra of these disaccharides, **2** and **3**, were shown in Table 1 with those of **1**.[1] The results revealed that the chemical shifts and splitting patterns of the respective protons in **2** were almost identical with those of **1** rather than those of **3** except

Table 1. Comparison of ^{1}H-NMR chemical shifts (δ) and coupling constants (J-values in Hz) of in the sugar part of natural polycavernoside-A (**1**) and the synthetic disaccharides (**2** and **3**).

	Polycavernoside-A (**1**)	 **2**		 **3**	
position	$\delta_1{}^a$	$\delta_2{}^b$	$\lvert\delta_1-\delta_2\rvert$	$\delta_3{}^b$	$\lvert\delta_1-\delta_3\rvert$
1	4.32 (d, 8)	4.12 (d, 7.6)	0.2	4.12 (d, 7.7)	0.2
2	2.88 (dd, 8, 10)	2.90 (dd, 7.5, 9.1)	0.02	2.80 (dd, 7.7, 9.2)	0.08
3	3.44 (t, 10)	3.44 (dd, 8.6, 8.9)	0	3.47 (dd, 8.8, 9.2)	0.03
4	3.13 (dt, 4, 10)	3.14 (ddd, 4.7, 8.7, 9.6)	0.01	3.26 (ddd, 5.1, 8.8, 10.5)	0.13
5ax	3.07 (t, 10)	3.08 (dd, 9.6, 10.9)	0.01	3.05 (dd, 10.5, 11.4)	0.02
5eq	3.93 (dd, 4, 10)	3.97 (dd, 4.5, 10.8)	0.04	3.97 (dd, 5.1, 11.4)	0.04
1'	5.21 (d, 4)	5.22 (d, 3.1)	0.01	5.31 (d, 2.6)	0.10
2'	3.36 (dd, 4, 11)	3.32~3.38 (m)		3.32~3.38 (m)	
3'	3.37 (d, 11)	3.32~3.38 (m)		3.32~3.38 (m)	
4'	3.79 (br s)	3.79 (br s)	0	3.79 (br s)	0
5'	4.13 (q, 7)	4.13 (q, 6.6)	0	4.13 (q, 6.6)	0
6'	1.07 (d, 7)	1.07 (d, 6.6)	0	1.07 (d, 6.6)	0
OH	2.66 (d, 3)	2.65 (br s)	0.01	2.65 (d, 2.9)	0.01

a) Yasumoto et al.[1]

b) ^{1}H-NMR spectra were measured at 400 MHz in CD_3CN (CHD_2CN as 1.9 ppm).



Reagents and conditions: a) NBS (1.2 eq), Et_3SiOTf (0.5 eq), CH_2Cl_2, -18 °C, 10 min, α-isomer (**14**, 65%) and β-isomer (13%); b) H_2, 10% Pd/C, MeOH, 18 °C, 59 h, 70%; c) NBS (1.2 eq), Et_3SiOTf (0.5 eq), CH_2Cl_2, -18 °C, 10 min, α-isomer (**15**, 68%) and β-isomer (29%); d) H_2, 10% Pd/C, MeOH, 18 °C, 14.5 h, 70%.

Scheme 2.

C-1. In view of the presumption that the tetrahydropyranyl moiety might attach taking an equatorial conformation to the xylose ring, the influence of the tetrahydropyran ring on the chemical shifts and splitting patterns of xylose part is supposed to be minor. Accordingly, we have concluded that the disaccharide moiety of **1** might consist of a combination of D-xylose and L-fucose or their enantioisomers.

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References and Notes

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