Total Synthesis and Absolute Configuration of Polycavernoside A

Kenshu Fujiwara and Akio Murai*

Division of Chemistry, Graduate School of Science
Hokkaido University, Sapporo 060-0810, Japan

Mari Yotsu-Yamashita and Takeshi Yasumoto*†

Faculty of Agriculture, Tohoku University
Tsutsumidori-Amamiyamachi Aoba-Ku
Sendai 981-8555, Japan

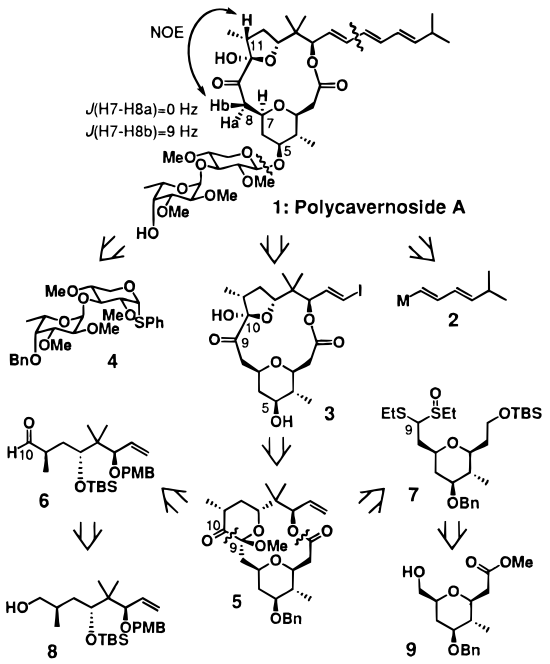
Received July 10, 1998

Polycavernoside A (**1**) was isolated as a causative toxin of sudden and fatal human intoxication in Guam in 1991[1] by Yasumoto's group from the red alga *Polycavernosa tsudai*, which had been eaten widely without any problems.[2] The planar structure of **1** has been proved to be a novel 13-membered macrolactone disaccharide possessing a triene moiety. However, because of the natural scarcity of the compound, stereochemical information obtained so far has been limited to the partial relative structures of each sugar component and bottom (C1−C8) and upper halves (C9−C15) of the macrolactone part. Later, Murai's group determined the relative configuration of the sequence of the fucose−xylose bottom half of the macrolactone synthetically,[3a] but the absolute configuration was still unknown. From the viewpoint of public health at algal feeding areas, clarification of the absolute structure is important; such information may promote a solution to the puzzling outbreak of the intoxication and explain the strong bioactivity. In this paper, we report the first total synthesis of **1** and determination of the absolute configuration.

Before planning of the synthesis, we deduced the whole molecular structure of **1** as shown in Scheme 1, based on the following points: (1) anti conformational relationship between H7 and H8b suggested by large $^3J_{H7/H8b}$ value (9 Hz) and no observation of NOE between H7 and H8b;[2c] (2) same-side placement of H8b and H11 on the macrolactone ring suggested by the presence of NOE between H8b and H11 and the absence between H8a and H11;[2a] (3) natural predominance of D-xylose and L-fucose in marine biota.

Our synthetic plan is outlined in Scheme 1. Introduction of the triene, considering its potential lability, was scheduled in the final step after the glycosylation of lactone **3** with **4**[3a,4] derived from L-fucose and D-xylose. Hydrolytic reconstruction of the acetal moiety of **5** within the framework of lactone was expected to set up the stereochemistry at anomeric C10 of **3** in natural form. Further, this strategy would also rely on the successful lactonization to **5** from the requisite secoic acid, the stereoselective formation of six-membered cyclic methyl acetal, and the connection of the acyl anion equivalent[5] derived from **7** with aldehyde **6** at the C9−C10 bond. For the preparation of **6** and **7**, alcohols **8**[3d] and **9**[3c] would be available, respectively.

Scheme 1



The diethyldithioacetal mono-*S*-oxide **7** was readily obtained in seven steps from alcohol **9** (Scheme 2). Swern oxidation[6] and subsequent Wittig reaction provided a methyl vinyl ether in 90% yield, which was hydrolyzed under acidic conditions to give aldehyde **10** (92%). Then, Evans' thioacetalization,[7] reduction of the methyl ester, protection of the resultant alcohol with TBS, and selective oxidation of the thioacetal moiety afforded monosulfoxide **7** in 92% overall yield.

Deprotonation of **7** with LDA (1 equiv) in THF at −78 °C followed by addition of aldehyde **6** (0.5 equiv), derived from **8** by Swern oxidation,[6] provided acid-sensitive dithioacetal **12**[8] (a mixture of diastereomers, 46% based on **6**) and vinyl sulfide **13**[8,9] (a single diastereomer, 33% based on **6**) together with recovered **7** (57%) and **6** (17%). When the adduct **12** was treated with *p*-toluenesulfonic acid in MeOH−$(MeO)_3CH$ (10:1), removal of the ethylthio and ethylsulfinyl groups, desilylation, and cyclic methyl acetal formation occurred in one pot to produce the desired bicyclic compounds **14**[10] (50%) and C9-epimeric **15**[10] (18%). Under the same conditions, vinyl sulfide **13** was transformed into **14** in 65% yield. Swern oxidation[6] of diol **14** and the following removal of PMB[11] provided keto aldehyde **16** (81%). Secoic acid **17**, obtained after $NaClO_2$ oxidation[12] of **16**, was lactonized smoothly by modified Yamaguchi's method[13] to give 12-membered lactone **5** in >75% yield.

† Present address: Japan Food Research Laboratories, Tama Laboratory, 6-11-10, Nagayama, Tamashi, Tokyo 206-0025, Japan.

(1) Haddock, R. L.; Cruz, O. L. T. *Lancet* **1991**, *338*, 195−196.

(2) (a) Y.-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147−1148. (b) Y.-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563−5566. (c) Y.-Yamashita, M.; Yasumoto, T.; Haddock, R. L. *34th Symposium on the Chemistry of Natural Products (Tokyo)*, Symposium Abstracts, 1992; pp 612−619.

(3) (a) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 855−856. (b) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 191−192. (c) Fujiwara, K.; Amano, S.; Oka, T.; Murai, A. *Chem. Lett.* **1994**, 2147−2150. (d) Hayashi, N.; Mine, T.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1994**, 2143−2146.

(4) For another synthesis of the sugar part of polycavernoside A: Johnston, J. N.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 4341−4344.

(5) Herrmann, J. L.; Richman, J. E.; Wepplo, P. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 4707−4710.

(6) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482. (c) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(7) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009−5017.

(8) Dithioacetal **12** and vinyl sulfide **13** were purified by chromatography using silica gel doped with 4% Et_3N.

(9) **13** was gradually produced from some of the diastereomers of **12** under the reaction conditions (checked by TLC analysis). The other diastereomers of **12** were unchanged for prolonged periods under the same conditions.

(10) The axial orientation of each methoxy group at C9 of **14** and **15** was confirmed by the existence of NOE between H13 and CH_3O at C9 in the derivative of **14** and the intact **15**, respectively: see Supporting Information.

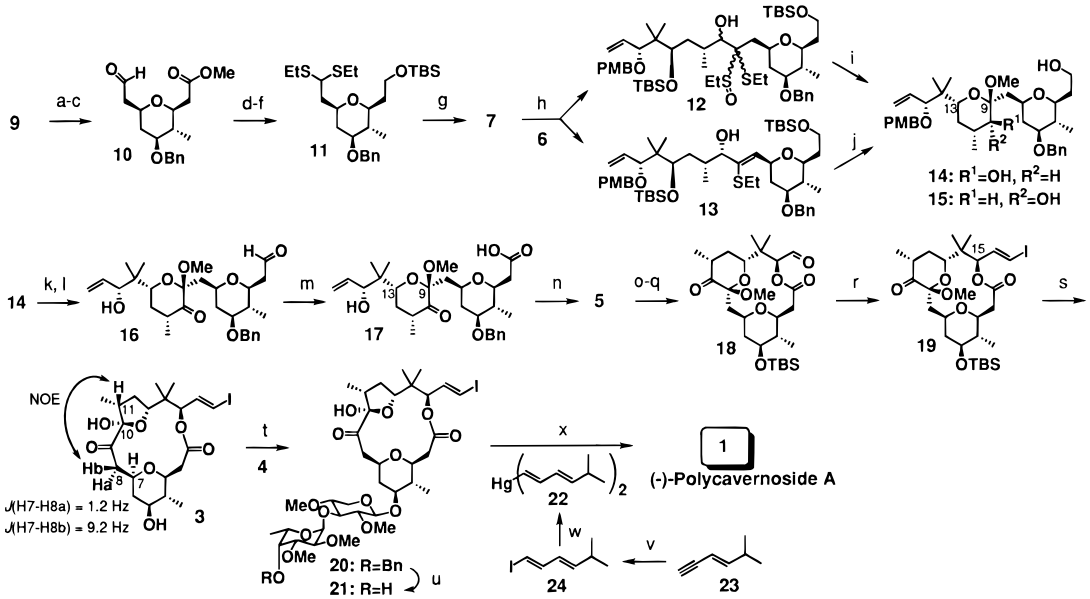
(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

(12) Kraus. G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176.

(13) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. For the efficiency of excess DMAP in the method: (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9. (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613−4628.

10.1021/ja982431b CCC: $15.00
Published on Web 10/03/1998

Scheme 2[a]



[a] Reagents and conditions: (a) $(COCl)_2$ (1.5 equiv), DMSO (2.4 equiv), CH_2Cl_2, −78 °C, 20 min, then Et_3N (5 equiv), −78 → 0 °C; (b) $Ph_3P{=}CHOCH_3$ (1.5 equiv), THF, −78 °C, 5 min, then 20 °C, 16 h, 90% from **9**; (c) THF−H_2O−TFA (1:1:0.2), 20 °C, 4.5 h, 92%; (d) TMSSEt (3 equiv), ZnI_2 (cat.), CH_2Cl_2, 20 °C, 5.5 h; (e) $LiAlH_4$ (2 equiv), THF, 0 °C; (f) TBS-Cl (1.1 equiv), imidazole (2.2 equiv), DMF, 0 °C, 99% from **10**; (g) *m*-CPBA (1 equiv), CH_2Cl_2, −60 °C, 93%; (h) LDA (1 equiv), THF, −78 °C, 10 min; then **6** (0.5 equiv), −78 °C, 30 min, 46% of **12** from **6**, 33% of **13** from **6**, 57% recovery of **7**, 17% recovery of **6**; (i) $TsOH{\cdot}H_2O$ (0.4 equiv), MeOH−$(MeO)_3CH$ (10:1), 25 °C, 21 h, 50% of **14**, 18% of **15**; (j) $TsOH{\cdot}H_2O$ (0.4 equiv), MeOH−$(MeO)_3CH$ (10:1), 25 °C, 3 days, 65% of **14**; (k) $(COCl)_2$ (10 equiv), DMSO (16 equiv), CH_2Cl_2, −60 °C, 20 min, then Et_3N (34 equiv), −60 → 0 °C, 88%; (l) DDQ (1.5 equiv), CH_2Cl_2, 20 °C, 2.5 h, 92%; (m) $NaClO_2$ (5 equiv), NaH_2PO_4 (10 equiv), 2-methyl-2-butene (100 equiv), *t*-BuOH−H_2O (3.5:1), 0 °C, 20 min, 100% (crude); (n) 2,4,6-trichlorobenzoyl chloride (4 equiv), Et_3N (8 equiv), THF, 20 °C, 10 h, then DMAP (37 equiv), toluene, 60 °C, 1 h, >75%; (o) OsO_4 (0.2 equiv), NMO (12 eq), 1,4-dioxane−H_2O (3:1), 20 °C, 31 h, then $NaIO_4$ (15 equiv), 40 min, >75%; (p) H_2, Pd/C, MeOH, 20 °C, 40 min; (q) TBSOTf (10 equiv), 2,6-lutidine (25 equiv), CH_2Cl_2, 0 °C, 5 min, >95% (2 steps); (r) $CrCl_2$ (270 equiv), CHI_3 (90 equiv), THF, 0 °C, 30 min, >80%; (s) THF−H_2O−TFA (2.5:2.5:1), 20 °C, 6.5 h, >95%; (t) **4** (4 equiv), NBS (8 equiv), MS4A, CH_3CN, −20 °C, 5 min, >50%; (u) DDQ (30 equiv), CH_2Cl_2−H_2O (25:1), 20 °C, 10 h, >70%; (v) *t*-BuLi (2 equiv), Et_2O−THF (1:1), −78 °C, 30 min, then $HgCl_2$ (0.5 equiv), −78 → 0 °C, 30 min, 100% (crude); (w) Cp_2ZrCl_2 (1 equiv), $LiEt_3BH$ (1 equiv), THF, 20 °C, 1 h, then **23**, 30 min, then I_2 (1 equiv), 58%; (x) **22** (excess), $Pd(PPh_3)_4$ (cat), THF, 0 → 20 °C, >75%.

Toward the final construction of the triene part, introduction of the *trans*-iodovinyl group was necessitated at this stage. Dihydroxylation of the vinyl moiety of **5** followed by oxidative cleavage and replacement of benzyl to TBS led to aldehyde **18** in >70% overall yield. Chemo- and stereoselective iodovinylation of the aldehyde was achieved to produce **19** under Takai's conditions.[14,15] The 6-membered cyclic methyl acetal **19** was converted to the desired 5-membered cyclic hemiacetal **3** quantitatively under mild acidic conditions. Stereochemistry at C10 of **3** was confirmed by the existence of NOE between H11 and H8b which showed a large $^3J_{H7/H8b}$ (9.2 Hz) as seen in natural **1**.

Glycosylation of **3** with fucosylxylose derivative **4**[3a] was carried out according to Nicolaou's procedure[16] to give the desired β-glycoside **20** in >50% yield, in which the benzyl group was removed by DDQ[17] to afford **21**.

We selected the less nucleophilic dienyl mercury **22** as a diene segment in the final cross-coupling reaction[18] with **21** to avoid any side reactions toward the oxygen functional groups. Although a homocoupling reaction proceeded as a side reaction in this system,[18] the use of excess reagent could complete the cross-coupling reaction. Thus, excess **22**, prepared from known enyne **23**[19] through a one-pot hydrozirconation−iodination sequence[20] and sequential lithiation−transmetalation process, was treated with vinyl iodide **21** and a Pd catalyst to produce **1** in good yield.

The synthetic material displayed physical and spectral properties including ^1H and ^{13}C NMR, IR, UV, and FABMS, as well as toxicological property to mice,[2a,21] identical to the natural product. The CD spectrum of natural polycavernoside A was identical with that of synthetic **1** in pattern, sign, and wavelength of each extreme point.[22] Thus, polycavernoside A has the absolute configuration of **1** shown in Scheme 1.

Acknowledgment. We are grateful to Prof. Y. Fukazawa, Hiroshima University, for valuable discussions. This work was supported by Grant-in-Aids from the Ministry of Education, Science, Sports and Culture, Japan (08245103 and 10308027, A.M.; 07780486 and 09780518, K.F.; 10760043, M.Y.-Y.), a Suntory Institute Bioorganic Research Grant, and a grant from the Naito Foundation.

Supporting Information Available: Experimental procedures and spectroscopic data for synthetic intermediates and CD spectra of natural and synthetic **1** (34 pages, print/PDF). See any current masthead page for ordering and Internet access instructions. See any current masthead page for ordering information and Web access instructions.

JA982431B

(14) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(15) The use of large excess reagents accelerated the reaction rate to prevent the epimerization at C15.

(16) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430−2434.

(17) For the related oxidative cleavage reactions of allyl and benzyl ethers: Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699−702.

(18) The cross-coupling reaction between alkadienylmercury and alkenyl halide for triene synthesis has not been reported. For cross-coupling reactions using alkenylmercury and arylmercury reagents: (a) Negishi. E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393−2401. (b) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551−564 and references therein.

(19) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1988**, *110*, 8223−8228.

(20) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257−7260.

(21) LD_{99} in mice (ip) of synthetic **1** was 240−360 μg/kg, while that of natural **1** was 200−400 μg/kg.

(22) CD spectral data of **1**: (natural) CD (CH_3CN, 22 °C) λ_{ext} 210.2 nm ($\Delta\epsilon$ 0.71), 227.8 (−0.15), 246.0 (0.21), 258.6 (0.03), 260.8 (0.15), 269.6 (−0.63), 280.4 (−0.65), 299.0 (−0.78); (synthetic) CD (CH_3CN, 22 °C) λ_{ext} 212.0 nm ($\Delta\epsilon$ 0.32), 228.8 (−0.25), 248.0 (0.19), 260.0 (−0.12), 262.8 (0.15), 268.6 (−0.42), 279.6 (−0.55), 299.8 (−0.73). Optical rotation data of **1**: (natural) $[\alpha]^{22}_D$ −59 (*c* 0.012, CH_3CN); (synthetic) $[\alpha]^{22}_D$ −66 (*c* 0.02, CH_3CN).